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FINAL REPORT

Contract No. DAMD17-83-C-3129
Multiple Animal Studies for Medical Chemical Defense
Program in Soldier/Patient Decontamination and Drug Development

on

TASK ORDER 84-8: ASSESSMENT OF SUBCUTANEOUS LETHALITY OF MUSTARD AND EFFICACY OF ENZYME INHIBITORS AGAINST MUSTARD LETHALITY IN THE MOUSE

Best Available Copy

to

U.S. ARMY MEDICAL RESEARCH
AND DEVELOPMENT COMMAND
INSTITUTE OF CHEMICAL DEFENSE

December, 1988

by

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Exposure to sulfur mustard (HD) may introduce cross-linkages and breaks into DNA strands, which if not repaired, can results in cell death. Hypothetically, excessive activation of the DNA repair enzyme, poly(ADP-ribose) polymerase, following HD exposure results in the depletion of oxidized nicotinamide adenine dinucleotide (NAD+), a cofactor essential for maintaining cellular viability. To test this hypothesis, the influence of three poly(ADP-ribose) enzyme inhibitors; 3-aminobenzamide (3AB), nicotinamide (NIC), and nicotinic acid (NA) was examined on the lethality and hematologic effects of subcutaneously administered HD using male, CD-1 mice. Two subcutaneous HD challenge doses approximating either the LD30 (22.0 mg/kg) or LD60 (28.2 mg/kg) were administered to groups of mice receiving intraperitoneal doses of each enzyme inhibitor. Three different inhibitor dose levels were tested at different administration time combinations relative to the HD challenge. Only 3 AB exhibited a significant ($P < 0.05$) effect in lowering HD mortality. This effect did not, however, appear to be dose-dependent over the range tested and appeared to be dependent on the time of administration.

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FINAL REPORT

on

TASK ORDER 84-8:
ASSESSMENT OF SUBCUTANEOUS LETHALITY
OF MUSTARD AND EFFICACY OF ENZYME
INHIBITORS AGAINST MUSTARD LETHALITY
IN THE MOUSE

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U.S. ARMY MEDICAL RESEARCH
AND DEVELOPMENT COMMAND
INSTITUTE OF CHEMICAL DEFENSE

December, 1988

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ASSESSMENT OF SUBCUTANEOUS LETHALITY OF MUSTARD AND EFFICACY OF ENZYME INHIBITORS AGAINST MUSTARD LETHALITY IN THE MOUSE

1.0 INTRODUCTION

The mutagenic and lethal effects of sulfur mustard (HD) have been attributed to the bifunctional cross-linking of DNA strands (thus preventing DNA replication) and monofunctional alkylation of DNA bases. The spontaneous depurination of the DNA bases may result in lesions that, unless repaired, become sources of transitional errors during replication.(1) Almost all DNA lesions are acted on by excision-repair nucleases in the cell's attempt to repair them. Thus, whether a lesion becomes detrimental is largely determined by the efficacy of the repair process.

Workers at the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) have proposed that, at HD doses resulting in extensive DNA strand breaks, the chromosomal repair enzyme poly(ADP-ribose) polymerase is activated to a degree that depletes the cellular content of oxidized nicotinamide adenine dinucleotide (NAD+).(2) Since NAD+ is the cell's primary electron transporter, depletion of NAD+ results in decreased glycolysis and respiration and eventual cell death. This mechanism for HD toxicity was based on evidence of increased urine levels of nucleic acid and nicotinamide (NIC) derivatives in rats exposed to nitrogen mustard (HN2).(3) Further, a single intraperitoneal (i.p.) dose (350 mg/kg) of NIC, which at high concentrations inhibits poly(ADP-ribose) polymerase, stimulated DNA repair and ameliorated pancreatic carcinogenesis in hamsters exposed to an HD-like alkylating agent.(4)

Task Order 84-8 ("Assessment of Subcutaneous Lethality of Mustard and Efficacy of Enzyme Inhibitors Against Mustard Lethality in the Mouse") was initiated in October 1984 at the Medical Research and Evaluation Facility (MREF) at West Jefferson, Ohio, to assess the mortality resulting from HD administered subcutaneously (s.c.) to mice, to establish a dose-response curve, and to assess the prophylactic/therapeutic effects of three candidate poly(ADP-ribose) polymerase inhibitors. MREF Protocol 18 (entitled "Assessment of Subcutaneous Lethality of Mustard in the Mouse") was used to define doses of HD (approximately LD_{20}, LD_{50}, and LD_{80}) that were subsequently used to determine the efficacy of administering NIC, 3-aminobenzamide (3AB), or nicotinic acid (NA) in inhibiting the toxic effects of HD through single and multidose regimens in MREF Protocol 19 (entitled "Evaluation of Potential Therapeutic Effects of Inhibitors Against Mustard in Mice").

Draft protocols were submitted to the USAMRICD in May 1984 for comment, modification, and subsequent approval for implementation at the MREF. Work began in October 1984 and MREF Protocols 18 and 19 were revised November 12, 1984, and signed February 15, 1985. Clinical work under MREF Protocol 19 ended in May 1986.

USAMRICD indicated in the Task Order 84-8 assignment document that statistical analyses concerning the evaluation of efficacies of the candidate inhibitors would be performed by USAMRICD personnel. During a visit to the MREF on August 1, 1985, Mr. Floyd Brinkley (USAMRICD Technical Monitor) outlined statistical tests to be performed by Battelle on mortality results at the end of the study. A formal request was made in June 1986 that specified the statistical analyses to be performed in Task Order 84-8. After further clarification, Battelle submitted a proposal describing the requested methods and estimating the costs and levels of effort. The proposed work was awarded as an extension of scope in Task Order 84-8 in September 1987 and the statistical analyses were commenced in September 1987. Copies of the signed protocols are included as Appendix A.

2.0 MATERIALS AND METHODS

2.1 ANIMALS

Male albino CD-1 mice were chosen for this study on the basis of their availability, cost, ease of handling and housing, and the fact that previous data on s.c. toxicity of HD had been generated using this species. Male albino CD-1 mice, 21 to 24 g, were purchased from Charles River Breeding Laboratories (Kingston, NY). All animals were quarantined at the Battelle Animal Resources Facility at 505 King Avenue before being transported to the MREF. Upon receipt, the animals were weighed, sexed, and ear tagged for positive identification, and observed for signs of disease during a quarantine period of at least 7 days. Following quarantine, animals were transported to MREF and acclimated for at least 24 hr prior to being placed on study.

While in quarantine, mice were housed five per cage in polycarbonate cages on stainless-steel racks equipped with automatic watering systems. After arriving at the MREF, animals were individually housed in polycarbonate cages with water bottles. At both facilities, humidity was maintained at 50 percent (± 10 percent) and temperature at 70 F (± 5 F). Fluorescent lighting provided a light/dark cycle of 12 hr each per day. Purina Certified Rodent Chow and water were available _ad libitum_ at all times during quarantine and study.

Battelle's Animal Resources Facilities have been registered with the U.S. Department of Agriculture (USDA) as a Research Facility (Number 31-R-21) since August 14, 1967, and are periodically inspected in accordance with provisions of the Federal Animal Welfare Act. In addition, animals for use in research are obtained only from laboratory animal suppliers duly licensed by USDA. Battelle's statement of assurance regarding the Department of Health and Human Services (DHHS) policy on humane care of laboratory animals was accepted by the Office of Protection from Research Risks (OPRR), National Institutes of Health (NIH), on August 27, 1973, and has since been updated as requested by OPRR. Animals at Battelle are cared for in accordance with guidelines set forth in the "Guide for the Care and Use of Laboratory Animals" (DHHS Publication No. (NIH) 85-23), and/or in regulations and standards as promulgated by the Agriculture Research Service, USDA, pursuant to the Laboratory Animal Welfare Act of August 24, 1966, as amended (P.L. 89-544 and P.L. 91-579).

On January 31, 1978, Battelle's Columbus Division received full accreditation of its animal-care program and facilities from the American Association for Accreditation of Laboratory Animal Care (AAALAC). Battelle's full accreditation status has been renewed after every inspection since the original accreditation. MREF is a part of the facilities granted full accreditation.

2.2 PREPARATION OF ANIMALS FOR STUDY

On the day prior to dosing, mice in good physical condition (based on general appearance) were assigned using a computerized procedure to a treatment group based on homogeneity of group body weight. The dorsa of the backs of all animals assigned to the study were clipped over an area sufficiently wide to provide easy visualization of the s.c. HD injection site.

2.3 VEHICLE SELECTION

USAMRICD originally suggested that polyethylene glycol, molecular weight approximately 200 daltons (PEG 200), be used as the vehicle solvent for HD in these studies. Preliminary studies of PEG 200 alone, however, showed that it was too toxic, producing an unacceptably high mortality when injected s.c. at volumes planned for these studies (300 $\mu\ell$). In addition, these injections resulted in seepage of solvent from the injection site, thus presenting a potential safety hazard if mixed with HD. Also, the viscous consistency of PEG 200 resulted in the possibility for back-pressure buildup within the syringe and subsequent "blowback" of the contents onto the operator. Finally, PEG 200 dissolved the plastic needle hubs, causing a delivery and purity problem.

These problems precluded the use of PEG 200, and a search for a suitable replacement ensued. Parallel studies were conducted with PEG 200 and ethanol as vehicles to compare effectiveness of HD delivery, LD_{50} values, safety of use, economy of use, and time for dosing. Comparisons were conducted using non-toxic volumes of PEG 200 (50 $\mu\ell$) and absolute ethanol (25 $\mu\ell$), which made it necessary to use surety concentrations of HD rather than exempt levels as originally planned.

These studies showed that ethanol was a more acceptable vehicle than PEG 200 for the following reasons:

(1) Ethanol was easier and safer to administer, with less chance of back-pressure buildup and resultant "blowback" (separation of syringe and needle at the hub).

(2) Ethanol produced less seepage at the dosing site than did PEG 200.

(3) Ethanol did not dissolve the plastic needle hubs.

(4) Ethanol did not affect the HD LD_{50} values, since HD mortality profiles were not different for the two solvents at the reduced volumes in either series.

Based upon these studies, a decision was made by the USAMRICD Technical Monitor (Mr. Floyd Brinkley), USAMRICD COTR (LTC(P) Howard Johnson), and the MREF Manager (Dr. Ronald Joiner) to use the ethanol-based system for Task Order 84-8 studies of HD in mice.

2.4 EXPERIMENTAL COMPOUNDS

HD was supplied by USAMRICD, along with data regarding its purity, appropriate identification (batch number, lot number, state), and stability. Purity and stability were not confirmed by Battelle for HD stored at Battelle during the study. The following information was obtained for HD:

Purity	97.3%
Density	1.27 g/mℓ
Known Impurities (w/w)	1.2% (Dithiane)
Unknown Impurities	1.5%

Absolute ethanol was purchased from U.S. Industrial Chemicals Co. (Tuscola, IL). PEG 200 was purchased from Baker Chemicals (Phillipsburg, NJ). The candidate inhibitor 3AB was purchased from Sigma Chemical Co. (St. Louis, MO), and NIC and NA were purchased from Aldrich Chemical Co. (Milwaukee, WI). The following information was supplied with them:

	Lot No.	Purity (Percent)
Absolute Ethanol	HTI81D30	99+
PEG 200	811384	Unknown; 100 Assumed
3AB	124F-3812	Unknown; 100 Assumed
NIC	PL 1322CJ	99+
NA	1626BL	98

2.5 TREATMENT DESIGN

2.5.1 MREF Protocol 18 - Dose-Response Studies

Three 14-day LD_{50} determinations were conducted using groups of 10 mice per dose and s.c. dose levels of HD in ethanol ranging from 14.7 mg/kg to 52.0 mg/kg, selected from literature values provided by USAMRICD.(5) Sufficient numbers of groups (based on at least five values between 10 and 90 percent mortality) were used in each of the three replicates to produce an LD_{50} and confidence intervals.

Two replicate 30-day LD_{50} determinations were conducted using groups of 10 mice per dose at s.c. dose levels based on results from the 14-day studies. These HD doses in ethanol ranged from 18.5 mg/kg to 46.8 mg/kg. In each replicate, sufficient numbers of groups were used to produce an LD_{50} (based on at least five values between 10 and 90 percent mortality) and confidence intervals.

An initial calculation of the composite 30-day dose-response curve was based on the target HD dose levels and corresponding mortality rates. The calculated LD_{20} and LD_{50} levels were immediately implemented in MREF Protocol 19 inhibitor studies. A second composite probit calculation was later performed using HD dose concentrations determined analytically by gas chromatography (GC). This dose confirmation process involved diluting nominal dose volumes of the HD/ethanol dosing solutions in hexane and injecting each dilution into a GC. The calculation revealed that the doses actually administered in the inhibitor studies were more nearly the LD_{30} and LD_{60}, respectively, as explained in Section 3.2.1.1.

2.5.2 MREF Protocol 19 - Inhibitor Studies

Six separate experiments were conducted at all combinations of two HD doses (the LD_{30} and LD_{60} determined under MREF Protocol 18) and three candidate inhibitors of HD toxicity (3AB, NIC, and NA). For each experiment the dose groups were consistently designated by letter as shown in Figure 2.1 (see Appendix B).

Animals in Groups A, B, and C received ethanol s.c. as the vehicle control. Group A mice received saline by i.p. injection 1 hr before receiving ethanol s.c. Group B mice received inhibitor solution i.p. at the low level 1 hr before receiving ethanol s.c. Group C mice received inhibitor solution i.p. at the high level 1 hr before receiving ethanol s.c.

Group K mice served as the positive controls and received saline i.p. 1 hr before receiving HD s.c. Animals in Groups J, H, and E received inhibitor solution i.p. at the low level either 1 hr before, 1 hr after, or 1 and 4 hr after receiving HD s.c., respectively. Animals in Groups G, I, and D received inhibitor solution i.p. at the high level either 1 hr before, 1 hr after, or 1 and 4 hr after receiving HD s.c., respectively. Group F mice received inhibitor solution i.p. at the multilevel 1 hr before and 1 and 4 hr after receiving HD s.c.

Groups of 10 male mice each were used in all studies in which NIC was the inhibitor. In later studies that involved 3AB and NA, the size of HD positive control Group K was increased to 30 for improved sensitivity in direct multiple comparisons of other HD-dosed groups with Group K.

HD was administered s.c. in absolute ethanol at either the LD_{30} (22.0 mg/kg) or LD_{60} (28.2 mg/kg), using the methods for dosing and dose-site decontamination described in Section 2.6. Dose volumes for HD in ethanol were held constant at 25 $\mu\ell$ per 30 g of body weight. Animals in control Groups A, B, and C received the same absolute volume of ethanol s.c. as the heaviest animal in the HD-dosed groups.

Inhibitors were administered in sterile, normal (0.9 percent) saline (U.S.P.) at either a low, high, or multiple concentration as shown below. All solutions administered i.p. were adjusted to pH 7.4 with 10 N, 1 N, or 0.1 N NaOH to minimize concentration changes. The resulting solutions were millipore filtered to minimize the microbial load associated with inhibitor administration.

INHIBITOR SOLUTION DOSE (mg/kg)
ADMINISTERED PER I.P. INJECTION

Level	3AB	NIC	NA
Low	100	100	50
High	500	500	500
Multi	200	100	150

Inhibitor dose volumes were held constant at 100 $\mu\ell$ per 10 g of body weight for NIC and NA and, because of solubility limitations of 3AB in saline, at 300 $\mu\ell$ per 10 g of body weight for 3AB. Saline control animals in Groups A and K received the same absolute volume as the heaviest animal among the inhibitor-dosed groups.

In addition to the LD_{30} and LD_{60}, MREF Protocol 19 called for testing the inhibitors at a third HD dose level, the LD_{80}. However, in initial studies, dosed at 28.2 mg/kg, HD-dosed positive control K groups exhibited mortality rates consistently higher, by 17 to 23 percent, than the expected 0.50 (as noted earlier, the 28.2 mg/kg dose was found analytically to be the LD_{60}). Since the LD_{80} dose level was expected to produce an even higher mortality rate, a decision to limit the task scope to only the lower two doses was reached in consultation with USAMRICD personnel. Mortality rates from later LD_{60} studies confirmed this decision as appropriate. The number of mice used per group is presented by replicate in Table 2.1 of Appendix E.

2.6 APPLICATION OF HD

Mice were placed in the dosing hood after having their backs clipped to remove the hair coat. Doses were administered s.c. with a 100-$\mu\ell$ or 500-$\mu\ell$ syringe (with a 25- or 27-gauge needle) in the middle of the back. The injection site was decontaminated immediately after injection with 5 percent sodium hypochlorite (NaClO) and rinsed with distilled water. The mice were then placed in cages and left in the hood for a 10-min period. At the end of the 10-min period, the dose site was again decontaminated with 5 percent NaClO and rinsed with distilled water. The mice were then removed from the hood, singly housed in holding cages, and observed for the remainder of the study period.

2.7 MORTALITY EVALUATIONS

Mortality was recorded when observed throughout the holding period in each study. Mortality fractions were based on the number of deaths observed in each dose group over the observation period. Mortality data were used to establish dose-response curves to determine three HD doses each at which to evaluate the efficacy of NIC, 3AB, or NA through single and multidose regimens in MREF Protocol 19.

2.8 HISTOPATHOLOGIC EVALUATIONS

2.8.1 MREF Protocol 18 - Dose-Response Studies

Mice were not necropsied and no tissues were collected in the HD dose-response studies.

2.8.2 MREF Protocol 19 - Inhibitor Studies

A complete necropsy was performed on all mice not surviving to the end of the 30-day observation period. Mice that died outside of the normal workday schedule or on weekends were dissected and the tissues fixed with approximately 5 mℓ of a 10 percent neutral buffered formaldehyde solution injected into the peritoneal cavity. The entire carcass was then placed into a jar of the same fixative. Among the survivors in each group, three mice were randomly selected for scheduled necropsy at the termination of the respective study.

The following tissues were collected for possible histopathologic examination: HD injection-site skin, bone marrow (decalcified sternum and femur), liver, spleen, small and large intestines, thymus, mandibular and mesenteric lymph nodes, and abnormal tissue identified at necropsy. These tissues were stored in jars of 10 percent neutral buffered formaldehyde solution. Selected samples (as discussed below) were processed via standard paraffin embedding, microtomy, and staining with hematoxylin and eosin.

After all replicate studies involving NIC and NA had been completed, tissue samples from groups of mice (typically three per group per HD LD_{60} replicate) that survived to day 30 were processed and examined. In addition, tissues from 16 moribund or recently dead mice representing seven of the HD LD_{60}/NIC groups and two of the HD LD_{60}/NA groups were processed and examined. Because of the absence of evidence for therapeutic/prophylactic effects by the inhibitors, a joint decision by the USAMRICD COTR and the MREF Manager was made not to process or examine any more tissues.

2.9 HEMATOLOGY EVALUATIONS

2.9.1 MREF Protocol 18 - Dose-Response Studies

Blood samples were collected in the 30-day studies from the post-orbital venous sinus of two different mice from each group at 1, 2, 3, 4, and 5 days after HD injection or until death of the entire group. Selection of mice for blood sampling was made when animals were assigned to each treatment group during the pre-study randomization procedure. Whenever possible, blood samples were collected from animals that had not been previously bled. If on a given day all surviving animals in a group had been previously bled, the least recently bled animals were selected for bleeding on that day. Blood was obtained from the sinus by penetration with a hypodermic needle, through which an approximately 0.5-mℓ sample was allowed to drip into whole blood collection microtainer tubes (Becton-Dickinson, distributed by American Scientific Products, Obetz, OH) for transportation to the clinical pathology laboratory.

One blood smear was prepared for each animal by mixing 10 μℓ of sampled blood with a drop of newborn calf serum on a microscope slide. The blood smear was air-dried and fixed in absolute methanol, then stained with Wright-Giemsa stain on an Ames automatic slide stainer (Miles Laboratories, distributed by American Scientific Products, Obetz, OH). The stained slides were coded to permit scoring at 1000x (oil immersion) by an observer unaware of the animal's treatment group. The incidence of micronucleated cells among 500 polychromatic and 500 normochromatic erythrocytes was scored for each sample. Additionally, a differential white blood cell (WBC) count for each time interval was performed to evaluate transient leukopenia, leukocytosis, and/or agranulocytosis as a function of time and/or dose.

Absolute cell concentrations (count/volume of blood) of lymphocytes and segmented neutrophils were calculated as products of the total WBC concentration and the respective differential percentages.

2.9.2 MREF Protocol 19 - Inhibitor Studies

Blood samples were collected from two animals per group at 1, 2, 3, 4, 5, and 30 days after HD administration. The selection of mice for blood sampling was determined randomly at the time of assigning animals to groups before each study was started.

Approximately 0.5 mℓ of blood was obtained from the post-orbital venous sinus with a glass capillary tube. All other details concerning blood specimen processing and analyses were the same as described in Section 2.9.1.

2.10 STATISTICAL ANALYSES

Analyses of the data were made to calculate 14- and 30-day LD_{50} values (and confidence intervals) and to test for poolability of replicates. Data from all studies were combined to determine composite 7- and 14-day LD_{50} values.

2.10.1 MREF Protocol 18 - Dose-Response Studies

2.10.1.1 Mortality Data

The dose-response studies were conducted in a stage-wise fashion. Three replicates were performed for the 14-day LD_{50} studies, and two replicates were performed for the 30-day LD_{50} studies. LD_{50} estimates and associated confidence intervals were calculated separately for each replicate based on the two-parameter $\log_{10}$ probit model.(6) Composite LD_{50} estimates were also calculated using the two-parameter $\log_{10}$ probit model. Separate poolability tests were conducted for 14-day and 30-day replicates to determine whether each set was internally consistent for calculation of a composite LD_{50}.

The chi square method was used for poolability determinations. If the difference between the composite and replicate values was within acceptable limits, the null hypothesis (H_0:equality of dose-response relations among replicates) was accepted, and the data were pooled. If the data were not poolable, the individual dose-response relations were compared for consistency. If one replicate differed from the other two, which were in agreement, the inconsistent replicate was discarded and the procedure was repeated.

2.10.1.2 Hematology Data

Components of the differential count that consisted of practically all zero values (i.e., non-segmented neutrophils, monocytes, eosinophils, and basophils) were excluded from this report. The remaining responses included total WBC count, absolute lymphocyte count (ABSLYMPH), absolute segmented neutrophil count (ABSSEG), and incidence of micronucleation among 500 normochromatic red blood cells (MICNORM) and separately among 500 polychromatic red blood cells (MICPOLY).

Since HD dose levels were not identical across 30-day mortality study replicates, and because blood was sampled from only two animals from each group on a given day, an adequately sensitive statistical analysis of the hematologic data required the pooling of results from groups with proximal dose levels. The difference between the largest and smallest dose levels within a set of pooled groups did not exceed 2.5 mg/kg. This resulted in seven sets with unequal numbers of samples, i.e., from one to five groups per set as shown and identified in Figure 2.2 (Appendix B). The dose ranges for the seven sets are shown below:

COMBINATION OF GROUPS FROM TWO 30-DAY
DOSE-RESPONSE STUDIES INTO SETS
FOR SUBSEQUENT ANALYSIS OF HEMATOLOGY DATA

Set	Dose Range (mg/kg)	Dose(s) (mg/kg)	No. Groups per Set (Combined Replicates)
1	0	0.0	2
2	1 - 21	18.5, 20.6	2
3	22 - 25	22.7, 23.3, 24.6	3
4	26 - 28	26.1, 27.1	2
5	29 - 33	30.1, 30.2, 30.4, 31.7, 32.4	5
6	34 - 40	38.9	1
7	41 - 47	46.8	1

An initial review of the total WBC count data revealed several suspected outliers. Based on the known radiomimetic effects of HD,(7) it seemed unlikely that any mouse could sustain a WBC count of 10,000/$\mu\ell$ or more at 3 days after s.c. exposure to 20 mg/kg or more of HD. An outlier screen was applied to the total WBC count data. The outlier screen involved the two-sided method of Grubbs at $\alpha = 0.05$, and was incorporated in an SAS (Statistical Analysis System Institute, Inc., Cary, NC) algorithm that calculated the studentized residuals in a single-parameter regression model and identified and eliminated the most extreme outlier (if any) in either tail.(8) The program repeated itself until no outliers remained. For any animal whose WBC count on a given day was eliminated by the outlier screen, all hematology data on that day were omitted from subsequent analyses. Clinical observation records were reviewed to determine whether animals with high WBC counts exhibited signs of HD toxicity.

A chi square test for poolability of results from the two replicates was performed on all hematology variables. An 11-parameter multiple regression model was applied to each replicate and to the pooled replicates for confirmation and to compare variability in the hemograms between replicates. Details of this procedure are presented in Appendix C. Results of the 11-parameter multiple regression model performed on the pooled data set were used to determine significant ($P < 0.05$) HD dose and time effects and interactions. These results were used to determine which variables to analyze in the MREF Protocol 19 inhibitor studies.

2.10.1.3 Correlation of Mortality with Hematologic Variables

To determine whether mortality was associated with hematologic variables, correlation calculations were performed for the number of deaths on a given day versus the hematologic data from survivors of the same dose range. Plots were generated for significantly ($P < 0.05$) linear relationships containing at least five points.

2.10.2 MREF Protocol 19 - Inhibitor Studies

Statistical methods for the analysis of mortality data obtained from six separate experiments, one for each HD dose and inhibitor combination, and performed over 12 days (only HD-dosed groups were replicated) are detailed in Appendix D.

2.10.2.1 Mortality Data

No animals from the ethanol control Groups A, B, and C died during any of the inhibitor studies. Thus those groups were excluded from the analysis of mortality results. Mortality results from the HD-dosed groups were analyzed to determine the effect of replicate (i.e., day of experimentation), inhibitor level, and dosing regimen. The method used a categorical modelling procedure (SAS PROC CATMOD) to separately fit four linear models to the logit of the mortality rates. The first model checked for group effects in each replicate. The second model used data pooled between replicates for each experiment and looked for effects due to group, replicate, and group-by-replicate interaction. Output from the second model was used to compare each group with the control Group K to determine therapeutic effects. The third model examined the experimental design factors (replicate and inhibitor level and regimen) in general to determine overall treatment effects. The fourth model used the total amount of inhibitor administered to a group regardless of timing as the independent variable.

2.10.2.2 Hematology Data

The hematologic variables investigated for possible inhibitor effects were identified by results from the MREF Protocol 18 dose-response studies. They included total WBC count, ABSLYMPH, and ABSSEG. Examination of blood samples from the dose-response studies had eliminated from analysis the incidence of micronucleation among 500 normochromatic and polychromatic red blood cells (RBC).

Data from saline control groups and HD-dosed groups were analyzed separately using a general linear modelling procedure (SAS PROC GLM). For the saline control groups, a 12-parameter ANOVA was used to test for possible toxic effects of inhibitor alone. For the HD-dosed groups, three models were used separately to test for effects over the time course of each experiment. The first model tested for hemogram differences due to group, replicate, and interactions with time. The second model looked for association of the total amount of inhibitor administered regardless of regimen. The third model examined the experimental design factors (replicate and inhibitor level and regimen). Data were plotted for an experiment if any of these models revealed significant ($P < 0.05$) main effects, i.e., significant differences due to group, replicate, total amount of inhibitor, inhibitor level, or dosing regimen.

3.0 RESULTS

Tables are presented in Appendix E and Figures are presented in Appendix B. Since no blood samples were collected between days 5 and 30, the shape of the line(s) drawn in each figure over that recovery period should be ignored, since the rate of recovery may not be accurately represented by the line(s).

3.1 MREF PROTOCOL 18 - MORTALITY STUDIES

3.1.1 14-Day Dose-Response Studies

Seven HD-dosed groups of 10 male mice each were used in the triplicate 14-day LD_{50} studies. The dosages and corresponding mortality profiles for each HD group are given in Table 3.1 and plotted in Figure 3.1. The LD_{50} for the first replicate was 26.8 mg/kg, with a lower 95 percent confidence limit of 23.4 and an upper limit of 30.9. The slope of the curve was 6.24. The second replicate had an LD_{50} of 32.3 mg/kg, with a lower limit of 27.5 and an upper limit of 40.9; the slope was 4.99. The third replicate had an LD_{50} of 30.6 mg/kg, with a lower limit of 28.0, an upper limit of 33.5, and a slope of 11.4.

The test of poolability showed the data from all three replicates to be consistent and statistically similar. The composite LD_{50} was 29.4 mg/kg, with a lower limit of 27.4 and an upper limit of 31.7. The slope for the composite 14-day LD_{50} was 6.59, plus or minus one standard error of 0.78. A summary of the 14-day LD_{50} results is presented in Table 3.2.

3.1.2 30-Day Dose-Response Studies

Six HD-dosed groups and one vehicle control group of 10 male mice each were used in the duplicate 30-day dose-response studies. The doses and corresponding mortality profiles for each HD group are given in Table 3.3 and plotted in Figure 3.2. The LD_{50} for the first replicate was 26.2 mg/kg, with a lower 95 percent confidence limit of 21.3 and an upper limit of 29.1. The slope of the curve was 7.53. The second replicate had an LD_{50} of 27.0 mg/kg, with a lower limit of 24.1, and an upper limit of 33.0; the slope was 6.58.

The test of poolability showed the data from both replicates to be consistent and statistically similar. The composite LD_{50} was 26.5 mg/kg, with a lower limit of 24.4, and an upper limit of 28.5. The slope for the composite 30-day LD_{50} was 7.30, plus or minus one standard error of 1.33. A summary of the 30-day dose-response studies is presented in Table 3.4.

3.1.3 Composite LD_{50} Values

Composite 7-day and 14-day LD_{50} values were calculated by combining data from all three 14-day replicates and both 30-day replicates. This gave a sample size of 350 animals. The doses and corresponding mortality fractions for the 7-day and 14-day composite values are given in Table 3.5 and plotted in Figures 3.3 and 3.4. The LD_{50} for the composite at 7 days was 29.3 mg/kg, with a lower 95 percent confidence limit of 27.7 and an upper limit of 31.1. The slope of the curve was 6.13, plus or minus one standard error of 0.63. The LD_{50} for the composite at 14 days was 28.0 mg/kg, with a lower 95 percent confidence limit of 26.6 and an upper limit of 29.6. The slope of the curve was 6.68 plus or minus 0.66. A summary of the composite dose-response results is presented in Table 3.6.

3.1.4 Hematology Results

Results to confirm poolability of the replicates and to determine whether the 11-parameter ANOVA model adequately described the hematology data are presented in Table 3.7. The test for replicate poolability indicated that, for all hematologic variables except MICPOLY, combination of the data across replicates was not warranted. Thus these results conflict with the mortality data, which were poolable. There was no apparent reason that the mortality rates were similar across replicates but the hemograms were not. The data in Table 3.7 show that the 11-parameter ANOVA model fits the data for each of the hematologic variables. Based on the fit for mortality and the 11-parameter ANOVA model, the hematology data were pooled for subsequent analyses.

The hematology results for individual animals on each day of blood sampling are presented by HD dose level in Table 3.8 for both replicates of the 30-day study. Three outlier WBC counts were identified, all from the second replicate. Two of the outlier data were from animal M729M, and the other was from animal M665M. Although dosing records did not show any noticeable bleeding from either animal's injection site after dosing, neither animal exhibited any of the typical, acute clinical signs associated with s.c. HD toxicity (e.g., injection site necrosis and edema). The clinical and hematologic evidence indicated that these animals were not properly dosed. Thus, all data for those animals were removed from the data set.

All other data were combined across replicates in sets of groups having dose levels ranging no more than 2.5 mg/kg from each other (Section 2.10.1.2). Mean values, standard deviations, and the number of animals represented are given by set in Table 3.9 for five hematology responses pooled across replicates. The mean incidence of non-segmented neutrophils, monocytes, eosinophils, basophils, and nucleated RBC were excluded from Table 3.9 because of their almost total absence in the samples examined. Means for the five variables are also presented from Figures 3.5 through 3.9. Significant ($P < 0.05$) factors determined from the 11-parameter regression model performed on the five hematologic variables are identified in Table 3.10. The significant factors were classed into three levels, i.e., $0.05 > P > 0.01$, $0.01 > P > 0.001$, and $P < 0.001$. The intercept parameter was significant at the 0.0001 level for all variables. This indicated that the intercept for each variable was non-zero and as such was ignored. The analysis indicated that, averaged across all 5 days, the trend of ABSLYMPH decreasing with increasing HD doses was significantly linear and quadratic. Also, the quadratic relationship of ABSSEG versus HD dose was day-dependent, which reflected the fact that on day 1 the control mean was at the lowest level among the set means, whereas after day 3 the control mean was at the highest level. In addition to ABSLYMPH and ABSSEG, the WBC count was included as a variable for investigation in the inhibitor studies because it best reflected the overall health of the animals.

At 24 hr after HD dosing, the mean total WBC counts for all dose ranges were less than the mean for the controls. A general trend of leukopenia prevailed in all HD-dosed sets over the 5-day observation period, although the statistical test for dose effects was not significant ($P > 0.05$). The failure of the test to detect a difference that was visually apparent was probably due to the low power of the test resulting from the small sample size of two blood samples per group per day.

All treatment group sets at 24 hr after dosing exhibited lymphopenia and a concurrent increase in ABSSEG relative to controls. From 1 to 5 days after dosing, ABSLYMPH of HD-dosed group sets was approximately 20 percent of the controls. The ABSSEG means generally decreased for all HD-dosed group sets from day 1 to day 5, whereas the controls increased from day 1 (740/μL) to day 2 (2,360/μL), decreased on days 3 and 4 (800/μL and 710/μL, respectively), and recovered to 1,260/μL by day 5. Despite the differences in trends observed for ABSSEG, the effect of HD dose was not significant ($P > 0.05$).

The mean MICNORM among HD-dosed groups was generally greater than that for the controls (which ranged from 0.5 to 1.0 per 500 cells), although the trends with dose were not significant ($P > 0.05$). The mean MICPOLY among HD-dosed groups was also generally greater than that for the controls (which ranged from 0.67 to 1.75 per 500 cells), although the trends with dose were again not significant ($P > 0.05$). There was an increase in the latter variable at day 2 among the mid-range group sets, but not enough to be statistically significant when averaged with the other days. The day 2 effect did not appear to be dose-related.

3.1.5 Correlation of Hematology with Mortality Results

Results of the correlation test of daily mortality as a linear function of each hematologic variable are summarized in Table 3.11. Significant ($P < 0.05$) regression plots containing at least five points are presented in Figures 3.10 through 3.15.

WBC count was negatively correlated ($P < 0.05$) with daily mortality at the 26 to 28 and 29 to 33 mg/kg dose ranges. This implied that low total leukocyte count for a group was associated with high death rates for that group.

ABSLYMPH was positively correlated with daily mortality at the 22 to 25 mg/kg dose range. The equivocacy ($P = 0.0486$) of this correlation, coupled with the lack of correlation in any other dose range, places in doubt the value of lymphocyte concentration as a predictor of mortality.

ABSSEG was negatively correlated with daily mortality at the 22 to 25, 26 to 28, 29 to 33, and 34 to 40 mg/kg dose ranges. This implies that loss of neutrophils was more closely associated with mortality than was total WBC count. The slope of the regression plots became increasingly negative with increasing dose (see Figure 3.16), which implies that higher daily mortality rates were reached at low neutrophil counts in the high HD dose ranges than were achieved in the low HD dose ranges. Since the correlation test determines only association and not causality, two correlated variables may be independent of each other but directly determined by a third variable. That is, the daily mortality rates may have been determined more (or at least in part) by an unknown third variable rather than directly by low neutrophil count.

There were no significant correlations of MICNORM with daily mortality rates.

MICPOLY data from 4 days were positively correlated ($P = 0.0001$) with daily mortality at the 34 to 40 mg/kg dose range, but the small sample size and lack of correlation in any other dose range places in doubt the value of MICPOLY as a predictor of mortality.

3.2 MREF PROTOCOL 19 - INHIBITOR STUDIES

3.2.1 Mortality Results

Group mortality profiles are presented for both replicates by target HD dose level and inhibitor in Table 3.12. Since there were no deaths observed during the observation period in any of the non-HD groups (A, B, and C), results for those groups are excluded from the remainder of this section.

The mortality rates for the HD-dosed groups are presented as block charts (mortality rate versus inhibitor regimen and level) for each replicate in Figures 3.17 through 3.28. For comparisons of inhibitor efficacies, the data are pooled between replicates and presented as block charts (mortality rates versus inhibitor and inhibitor level) in Figures 3.29 through 3.36. In both sets of figures, the mortality rates were truncated by the plotting program and are accurate to within 0.5 percent. In Figures 3.29 through 3.36, the base numbers are totals of mortality rates between replicates (instead of mean mortality rates) to emphasize that the replicates were generally not poolable.

3.2.1.1 Poolability of the Data Between Replicates

Comparison of the data in Table 3.12 disclosed an inconsistency between replicates within some experiments (HD dose level by inhibitor combinations). An analysis of means procedure was used to test for consistency in mortality rate among the six Groups K that received HD at the LD_{30} and separately among the six Groups K that received HD at the LD_{60}. Within each of the two sets of six groups, the animals were targeted to have been treated identically. The analysis revealed that at both the LD_{30} and LD_{60} of HD, the Group K mortality rates were inconsistent ($P < 0.05$). At the LD_{30}, the first replicate had a Group K mortality rate of 0.70, which was inconsistent with the mean of 0.40. At the LD_{60}, the first replicate had a Group K mortality rate of 0.33, which was inconsistent with the mean of 0.67.

A review of the HD dilution and dosing records revealed the reason for the inconsistency. During the first five inhibitor studies, the dilution concentration was checked analytically by GC on both days. If the concentration of HD was found to have changed, either a new solution was made, the dose volumes were increased, or HD was added to the dilution to bring the concentration up to the target level so that the total HD delivered would be at the target level. Thus if the analysis revealed an HD concentration of at least 90 percent of the expected value, the dilution was used without modification of the dose volumes.

On both August 16 and 19, 1985, an HD solution was analyzed at approximately 65 percent of the expected concentration. To avoid increasing the amount of ethanol administered by a factor of 1.54, undiluted HD was added to the solution. The resulting solution was analyzed at 96.5 percent of expected HD concentration, and the dose volumes were not adjusted because of the proximity of the analysis results to the target level. This was the LD_{30} replicate for which the Group K mortality rate (0.70) was inconsistent with the other five. Apparently the degraded (presumably hydrolyzed) HD retained some toxicity that contributed to the mortality rate. The addition of more HD to the solution brought the concentration of HD to the target level, but the total insult to the mice was significantly increased as well.

On Monday, October 14, 1985, an HD dilution was analyzed at 89 percent of expected. No adjustments in dose volume were made because of its proximity to the target level. This was the LD_{60} replicate for which the Group K mortality rate (0.33) was significantly inconsistent with the other five, presumably because for all subsequent replicates the dose volumes were adjusted upward so that the HD target dose was delivered. Apparently the mortality rates were increased by the upward adjustments of dose volumes due to some factor other than the amount of HD administered, which analytically was correct (the toxicity of degraded HD, presumably hydrolyzed by the hydroxyl group on ethanol, was probably this factor). At the time, the MREF analytical facilities did not include a mass selective detector for proving this hypothesis. Work performed since the conclusion of Task Order 84-8 has confirmed that HD is slowly hydrolyzed by ethanol.

The inconsistencies described above did not compromise the validity of the results because all groups within a replicate were dosed with the same HD solution, and the purpose of the tests was to determine the effect of inhibitors administered relative to HD control groups. Even though the HD dose was apparently not constant between replicates, if the effect of inhibitor did not vary significantly between replicates, i.e., no inhibitor by replicate interaction existed, the results could be pooled.

Comparisons of mortality rates between each replicate pair in an experiment are presented in Figures 3.37 through 3.42. Ideally, groups treated identically in replicate pairs would be expected to exhibit the same mortality rates, and the plotted values of these would all lie on a straight line passing through the origin with a slope of unity. Thus in Figures 3.37 through 3.42, the distance of each point from the line represents the difference in mortality between replicates for that group. Visual examination of the plots revealed that except for the HD LD_{60}/3AB experiment (Figure 3.40), there was a general inconsistency in treatment between replicates, especially for the HD LD_{30}/NIC (Figure 3.39) and HD LD_{60}/NA (Figure 3.42) experiments. The statistical significance of these apparent inconsistencies in dosing HD was tested as described below.

3.2.1.2 Results of Categorical Models

In the first test for poolability of replicate results, the general analysis revealed that there were no significant ($P < 0.05$) differences among HD-dosed groups in any of the replicates. For most groups, the effect of inhibitor treatment was in the same direction from Group K (had the same parameter sign) for both replicates, and in the cases when the effect was not in the same direction, the effect was not significant in either replicate. This suggested that the group-by-replicate interaction was not significant for any experiment, which would mean that the replicates could be pooled by experiment without obscuring any effects.

Results from the second categorical model, which used data pooled between replicates to check for group effects, confirmed that the group-by-replicate interaction was not significant ($P > 0.05$) in any experiment, thereby validating the pooling of data between replicates for enhanced sensitivity of the analyses. Results of this model are presented in Table 3.13. The replicate effect was significant ($P < 0.05$) for all experiments except HD LD_{60}/3AB, as is demonstrated in Figure 3.40. However, for all experiments the group-by-replicate interaction was not significant ($P > 0.05$), thereby validating the pooling of data between replicates.

Overall intergroup mortality rates were significantly ($P < 0.05$) different for the HD LD_{30}/3AB experiment only. Specifically, the total Group D mortality rate added across replicates (0.30) appeared lower than that for the Group K controls (0.77), and the Group G mortality rate sum (1.50) was greater than that of the controls, although these differences were not statistically significant when directly compared to the Group K controls by the subset procedure. These results indicated that the high level (500 mg/kg) of 3AB given at 1 and 4 hr after the HD dose was therapeutically beneficial, but that administering the same dose once at 1 hr before the HD dose was detrimental. Apparently, the dosing regimen was a significant factor at the high 3AB level.

In the HD LD_{60}/3AB experiment, the Group E mortality rate sum (0.90) was significantly ($P < 0.05$) lower than that for Group K (1.49), indicating a therapeutic effect at the low (100 mg/kg) 3AB level when administered at 1 and 4 hr after the HD insult. All groups were statistically identical ($P > 0.05$) in their mortality rates with the respective Group K in the NIC and NA experiments at both HD dose levels.

Results of the third categorical model, which was designed to detect inhibitor level and regimen effects in each experiment, are presented in Table 3.14. As suggested by the results of the second model, the inhibitor regimen effect was significant ($0.01 > P > 0.001$) for the HD LD_{30}/3AB experiment; i.e., mortality was decreased when 3AB was administered at 1 and 4 hr after HD and was increased when 3AB was administered at 1 hr before HD (see Figures 3.17 and 3.18). Also for that experiment, the level-by-regimen interaction was significant ($P < 0.05$), indicating that the regimen was significantly more important at the high 3AB level than at the low level. In the HD LD_{60}/3AB experiment, the regimen effect was significant ($P < 0.05$), as indicated by the downward trend in mortality rates from the "1 hr before" to "1, 4 hr after" positions presented in Figures 3.23 and 3.24. There were no apparent regimen effects in the other experiments.

Results from the fourth categorical model, which tested for the effect of the total amount of inhibitor administered regardless of timing relative to the HD dose, are summarized in Table 3.15 for each experiment. Mortality rates are presented versus total amount of inhibitor by experiment in Figures 3.43 through 3.48. The total amount of inhibitor administered was significant ($P < 0.05$) only for the HD LD_{30}/3AB experiment, in which the therapeutic effect of 500 mg/kg administered at 1 and 4 hr after the HD dose was previously suggested in Group D. In the HD LD_{60}/3AB experiment, the effect of total amount of 3AB was equivocally significant ($P = 0.0600$), reflecting the therapeutic effect of the same treatment (Group D). Otherwise, the amount of NIC or NA administered had no significant impact on mortality at either HD dose level. The total inhibitor-by-replicate interaction was not significant ($P > 0.05$) for any experiment, which indicated that the effect of increasing the amount of inhibitor had an equivalent effect in both replicates.

3.2.2 Histopathology Results

Histologic preparations of samples collected from 14 mice that became moribund or died during the HD LD_{60}/NIC study exhibited the following lesions: moderate to marked, diffuse, lymphoid and myeloid depletion of the spleen (13/14); moderate to severe, diffuse myeloid depletion of bone marrow (11/14); mild to severe, acute, focal or multifocal necrosis of the skin and/or subcutis (7/14); and mild to moderate, focal or multifocal necrosis of liver (3/14). Autolysis precluded adequate examination of many of the gastrointestinal samples. There was no apparent group-related pattern to these lesions. Group J (100 mg/kg NIC given at 1 hr before the HD dose) was not represented by any mice.

The HD LD_{60}/NA study was represented by tissues from only two mice, which exhibited splenic lesions of either necrosis or depletion.

All groups were represented by mice that survived to day 30 in the HD LD_{60}/NIC and HD/NA studies. Among control Groups A, B, and C, the only lesion observed was minimal to mild, acute, focal, or multifocal liver necrosis (1/6 per group). All lesions observed among the HD-dosed groups in either study were randomly distributed without any apparent association with treatment. These included: moderate to severe, active-chronic, focal skin ulceration (79/95) and/or inflammation (14/95); minimal to mild, sub-acute, focal or multifocal liver inflammation (12/95); and scattered adhesions to abdominal organs. Mild lymphoid and myeloid splenic depletion was observed in one Group H mouse from the NIC study.

3.2.3 Hematology Results

The raw hematology data for all groups are presented by experiment in Table 3.16. The three variables indicated for analysis by results of MREF Protocol 18 dose-response studies were total WBC count, ABSLYMPH, and ABSSEG. The analysis results for the no-HD Groups A, B, and C are presented separately from those for the groups dosed with HD.

3.2.3.1 Hematology Results for No-HD Groups

A summary of the hematology variables for the groups that did not receive HD is presented in Table 3.17. Results of the 12-parameter ANOVA model used to evaluate the possible toxic effects of each inhibitor on hematologic variables are summarized in Table 3.18. The level of NIC administered had a significant effect ($P < 0.05$) on each of the three leukocyte variables, but the significant interaction of level-by-dosing-day indicated that the effect was different for the HD LD_{30}/NIC versus the HD LD_{60}/NIC experiments. Figure 3.49 shows that the mean leukocyte count was greater in the higher level (Group C) mice relative to the lower level (Group B) mice on the day that the LD_{30} of HD was administered to Groups D through K. However, Figure 3.50 shows that on the first 4 days after the LD_{60} of HD was given, the lower inhibitor level group (Group B) exhibited an elevated WBC count relative to Group C. There was no apparent explanation for this interaction, except that by chance the Group B mice in the HD LD_{60}/NIC experiment may have had higher baseline WBC counts than the Group C mice. This is suggested by the day 1 means in Figure 3.50, and points out the need in possible future studies of using an animal model from which baseline samples may be collected for adjusting subsequent samples.

In the NA experiments, all three variables were significantly ($P < 0.001$) associated with the day of dosing, with WBC elevated in the HD LD_{60}/NA experiment over the HD LD_{30}/NA experiment. There was no apparent reason for this difference. The WBC means are presented for the HD LD_{30}/NA and LD_{60}/NA experiments in Figures 3.51 and 3.52, respectively. In the 3AB experiments, there was a significant ($P < 0.05$) cubic relationship of WBC and ABSLYMPH with time after dosing, although a plot of the mean ABSLYMPH data (Figure 3.53) did not appear to confirm this trend with time.

3.2.3.2 Hematology Results for Groups That Received HD

A summary of the hemogram data for the HD-dosed groups is presented in Table 3.19. The positive control Group K data were pooled across inhibitors for presentation by HD dose in Figures 3.54 through 3.59 for WBC, ABSLYMPH, and ABSSEG. The responses for the HD LD_{30} dose were similar to the same responses for the HD LD_{60} dose. Both mean WBC time courses exhibited a marked decrease from approximately 4,000/$\mu\ell$ on day 1 to 1,000/$\mu\ell$ on days 3 and 4, followed by a recovery period that was terminated on day 30 when the mean had reached 8,000 or 9,000/$\mu\ell$. Both mean ABSLYMPH time courses decreased from approximately 1,500/$\mu\ell$ on day 1 to approximately 800/$\mu\ell$ on day 3, followed by a recovery period to 4,000 to 5,000/$\mu\ell$ on day 30. Both mean ABSSEG time courses decreased from approximately 2,000 or 3,000/$\mu\ell$ on day 1 to nearly complete absence of neutrophils on days 4 and 5, followed by a recovery period terminated on day 30 at approximately 3,000/$\mu\ell$. For each hematologic response, the variability at day 30 was generally greater than on any other day.

The time courses of the hemograms of the inhibitor-dosed groups generally did not differ from the pattern of leukopenia just described, except that in some groups the initial decrease occurred before day 2. Therefore, the description of statistically significant effects that follows does not necessarily constitute a presentation of biologically significant effects.

The three ANOVA models used to analyze the hematology data among Groups D through K revealed results that were in close agreement. In all three models, the replicate effect was significant ($P < 0.01$) in the HD LD_{30}/NIC and HD LD_{60}/NIC experiments for WBC and ABSLYMPH; in the HD LD_{30}/NA experiment for WBC, ABSLYMPH, and ABSSEG; and in the HD LD_{60}/NA experiment for ABSLYMPH and ABSSEG.

The first ANOVA model detected no significant intergroup differences and no significant group-by-time interactions.

Results of the second ANOVA model, which evaluated the effect of the total amount of inhibitor administered, are presented for inhibitor main effects and interactions with time in Table 3.20. All main inhibitor effects were seen in the HD LD_{60}/NA experiment, in which WBC was significantly ($P < 0.05$) affected by the total amount of inhibitor administered, and WBC and ABSSEG were each significantly ($P < 0.05$) affected by the square of the total inhibitor amount. As shown in Figures 3.60 and 3.61 for WBC and ABSSEG, respectively, all HD-dosed groups exhibited a rapid loss of leukocytes from day 2 to days 3 and 4, followed by a slight recovery on day 5. On day 30, the mean WBC count was higher for each group than it had been on day 1. Since blood samples were not collected before the HD dose (to avoid periorbital infections), there is no assurance that the surviving animals were fully recovered by day 30. However, all HD-dosed groups exhibited mean WBC counts that were generally as high as the no-HD control counterparts, thus implying a full recovery. The significant inhibitor effects were apparently detrimental, since most other groups generally had lower WBC counts relative to the Group K controls.

There were no other significant main effects; however, in the HD LD_{30}/NIC experiment (as shown in Figure 3.62), all inhibitor-dosed groups exhibited larger mean WBC counts than did the Group K controls on days 4 and 5. The mortality rates from all inhibitor-dosed groups were generally lower than those in the Group K controls, although none of the specific contrasts or overall tests for differences were significant.

Results of the third ANOVA model, which evaluated the effect of inhibitor level and regimen, are presented for the main effects and level-by-regimen interaction in Table 3.21. There were no significant ($P < 0.05$) effects in the HD LD_{30} experiments for any inhibitor. At the LD_{60} of HD, the NA level effect and level-by-regimen interaction were significant for WBC. As previously shown in Figures 3.60 and 3.61, none of the treatments in that experiment prevented the onset of leukopenia, and graphically the effects of level and the level-by-regimen showed NA to be apparently detrimental to leukocytes. Also, at the LD_{60} of HD, the NIC level effect and level-by-regimen interaction were significant for ABSLYMPH. As shown in Figure 3.63, Groups D, G, and I, which were high-NIC-level groups, had generally higher ABSLYMPH means than did the other HD-dosed groups. These groups also exhibited the lowest mortality rates in the experiment, although no single group's mortality rate was significantly lower than that for the Group K controls, and the NIC level did not have a significant overall effect on mortality. There were no other significant main effects.

4.0 DISCUSSION

The studies completed under MREF Protocol 18 established an LD_{50} and mortality dose-response curves for HD administered s.c. to mice. Preliminary work with the model suggested ethanol as a satisfactory vehicle for HD in these studies. Ethanol was preferred over PEG 200 (originally designated in the protocol) because at the volumes used, ethanol was easier and safer to dose and had no apparent effect on mortality curves, and seepage at the dosing site was not observed.

Three replicates of 14-day LD_{50} studies using 210 mice and two replicates of 30-day LD_{50} studies using 140 mice produced composite 14-day and 30-day LD_{50} values of 29.4 and 26.5 mg/kg, respectively. Composite LD_{50} values for all mice at 7 days and 14 days were 29.3 and 28.0 mg/kg, respectively. In both 14- and 30-day studies, all mortalities occurred after day 1 and within the first 9 days after HD administration. Daily mortality rates appeared to be affected by dose level, with animals in high-dose groups dying more quickly than those in low-dose groups. Mortalities were generally at the highest level on days 6 and 7.

The associated 30-day mortality dose-response curves were used in determining the efficacy of administering 3AB, NIC, or NA in inhibiting the toxic effects of HD under MREF Protocol 19. From calculations based on mortality rates for analyzed HD doses, 22.0 mg/kg (the LD_{30}) and 28.2 mg/kg (the LD_{60}) were used in the inhibitor studies.

Hematology evaluations conducted in the 30-day dose-response study indicated dose-related leukopenia in HD-dosed mice for the duration of the 5-day sampling period. Histopathologic findings from the inhibitor studies indicated that the immediate effects of administering HD were lymphoid and myeloid tissue depletion in spleen, severe myeloid depletion in bone marrow, and an immediate reduction in circulating lymphocytes. Circulating neutrophils decreased in concentration from days 1 to 4, and apparently were not replaced from the bone marrow, as they died during that period. Expressed as relative percent populations of the total WBC count, the initial results of exposure to HD were relative neutrophilia and lymphopenia, followed by a reversal of proportions, to relative lymphocytosis and neutropenia. Examination of polychromatic red blood cells indicated an occasional high rate of micronucleation on day 2 that did not appear to be dose-related.

Schelegal and MacGregor demonstrated with six genotoxins (including HN2) that the frequency of micronucleation in normochromatic RBC can be significantly elevated in mice by five daily exposures to non-lethal doses.(9) In an earlier work, MacGregor et al. demonstrated a significant increase with a single 2.5 mg/kg dose of HN2.(10) However, they pointed out that overdosing with clastogens may completely decimate nucleated marrow cells, with total cessation of erythrogenesis for a period. They stated that such a delay would probably reduce the incidence of micronucleation in peripheral blood because many micronucleated cells would become normochromatic before reaching the peripheral circulation and would be diluted into the large number of irrelevant cells that had already matured before clastogen treatment. For routine genetic toxicity assays of micronucleated RBC in mice, Brusick recommended testing potential clastogens at two levels, i.e., at one half and at one twentieth the LD_{50}.(11) These doses would have been 13.3 and 1.3 mg/kg, respectively, according to the present dose-response study. However, in the present work the lowest doses administered in the dose-response and inhibitor studies were 18.5 and 22.0 mg/kg, respectively; these may have been enough to interrupt erythrogenesis without an increase in micronucleation.

There were no other significant dose- or time-related trends in any other variables measured in the hemograms from mice in the dose-response studies. Thus the hematologic variables selected for examination in the inhibitor studies were total WBC count and absolute lymphocyte and neutrophil concentrations. Daily mortality rates were negatively correlated with total WBC count and with absolute lymphocyte concentrations, which indicated that survivors of groups with high mortality rates on a given day exhibited a low leukocyte (specifically lymphocyte) count.

In the MREF Protocol 19 inhibitor studies, no animals died in any of the no-HD control groups that received saline, low-level inhibitor, or high-level inhibitor. Thus the effect of each inhibitor on mortality in the control groups was apparently inconsequential. Among the HD-dosed groups, mortality rates from replicate to replicate indicated inconsistent HD results. However, since the effect of each inhibitor treatment was statistically similar in both replicates relative to the positive HD controls, the data were pooled across replicates for analyses of various treatment effects.

Significant prophylaxis from HD toxicity as evidenced by mortality rates was observed for 3AB only. Overall intergroup differences and the effect of the total amount of inhibitor administered were significant in the HD LD_{30}/3AB experiment alone. Delayed, high-level treatments of 3AB seemed to increase the chances of mice surviving the HD LD_{30} insult ($P < 0.05$). Specifically, 500 mg/kg of 3AB administered at 1 and 4 hrs after the HD dose (Group D treatment) reduced the lethality rate to a mean of 15 percent from a mean control rate of 38 percent ($P = 0.0099$).

At the LD_{60} of HD, the administration of 100 mg/kg of 3AB at 1 and 4 hr after the HD dose significantly ($P < 0.05$) decreased mortality rate averages from approximately 75 percent in controls to 45 percent. Apparently the regimen used in administering 3AB was significant ($P < 0.05$); i.e., delaying 3AB treatments seemed to lower mortality rates. Since overall intergroup differences were not significant ($P > 0.05$), the results indicating a marginal prophylactic effect from delayed 3AB administration were considered inconclusive. However, coupled with the results of the HD LD_{30}/3AB experiment, the data indicated that the administration of 3AB appears to be marginally prophylactic to mice previously exposed to lethal doses of HD.

There were no significant NIC- or NA-treatment-related effects at either HD dose level.

Since the effects of 3AB treatment were level- and regimen-dependent, a comprehensive ranking of the inhibitors was not appropriate. However, among the four inhibitor regimens tested, dual treatment at 1 and 4 hr after the HD insult appeared to be the most prophylactic, especially when the inhibitor was 3AB. Lawson found that doses of NIC delivered after the clastogen insult were more effective than pre-insult doses in stimulating DNA repair in the hamster.(4) To explain this, he suggested immediate metabolism of NIC, interference by NIC on some late-stage DNA repair process, or alkylation of NIC by the clastogen as possible mechanisms.

The effects of inhibitors on the mice hemograms generally did not match the effects on mortality rates. There were no significant intergroup differences or group-by-time interactions in any experiment ($P > 0.05$). For all inhibitors, there were no significant effects of inhibitor level, regimen, or level-by-regimen interaction at the LD_{30} of HD, and there were no significant regimen effects at the LD_{60} dose level. Most surprising, there were no significant level, regimen, or interaction effects for 3AB at either HD dose. Thus the hematology results did not confirm the therapeutic effects by 3AB seen in the mortality results. Time plots of hematologic variables in experiments with statistically significant level and interaction effects (HD LD_{60}/NIC and HD LD_{60}/NA) revealed no biologically significant departures from the general pattern of acute leukopenia exhibited by the positive HD controls.

The only experiment with significant hematologic effects from using the total amount of inhibitor as the independent variable was the HD LD_{60}/NA experiment, in which most NA-treated groups generally exhibited lower leukocyte counts than the positive HD-dosed controls.

The general inconclusive nature of the hemogram analyses was likely due to a low power of test owing to small sample sizes (four per group per day). The statistical analysis also suffered from the design requirement that no baseline samples be collected. This was done so as not to inadvertently introduce microorganisms into the mice, thereby possibly altering the distribution of the hematologic variables from normality. The results of the analyses point out the need for a better animal model than the mouse because of the limit on how many blood samples can be collected without affecting an anemic response that may interact synergistically with HD toxicity. The experiment could be improved by increasing the number of animals in each group so that at least five blood samples are taken at each point by scheduled sacrifices.

5.0 RECORD ARCHIVES

Records pertaining to the conduct of the study are contained in Battelle Laboratory Record Book Nos. 40616 (analytical chemistry) and MREF-21, -25, -30, -37, -41, -47, -49, -53, -54, -57, -58, -59, -60, -64, -66, -67, -68, and -69 (*in vivo* studies). All prestudy animal quarantine and observation records are on file at the MREF.

All original data, as well as the original final report, will be maintained at the MREF until forwarded to USAMRICD at the conclusion of the project or until recorded on microfiche and permanently archived at Battelle.

6.0 ACKNOWLEDGMENTS

The names, roles in the study, and highest degrees of the principal contributors in this study are presented in the following list:

Name	Title	Degree
Dr. Ronald L. Joiner	Study Director	Ph.D.
Dr. H. Hugh Harroff, Jr.	Chief Veterinarian	D.V.M.
Thomas H. Snider	Study Supervisor	B.S.
W. Bruce Keys	Technical Supervisor	M.B.A.
Dr. Paul I. Feder	Biostatistician	Ph.D.
Ramona A. Mayer	Quality Assurance	B.A.

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APPENDIX A

MREF Protocol 18 --- "Assessment of Subcutanecus Lethality of Mustard in the Mouse" (Revised November 12, 1984)

MREF Protocol 19 --- "Evaluation of Potential Therapeutic Effects of Inhibitors Against Mustard in Mice" (Revised November 12, 1984)

Assessment of Subcutaneous Lethality of Mustard in the Mouse

Study Performed by Battelle Columbus Laboratories,
505 King Avenue, Columbus, Ohio 43201

1. Study Director: Ronald L. Joiner, Ph.D.

2. Veterinarian: H. Hugh Harroff, Jr., D.V.M.

3. Sponsor: U.S. Army Medical Research and Development Command

4. Sponsor Monitor: LTC Howard Johnson, USAMRICD

5. Objective:

The objective of the study is to determine the toxicity of HD administered subcutaneously in the mouse and to establish a dose-response curve. These data will be used to define doses of HD (e.g. LD20, LD50, LD80) to determine the efficacy of administering nicotinamide, 3-aminobenzamide, or nicotinic acid through single and multidose regimens in Protocol MREF-19.

6. Experimental Design:

A. Test System

(1) Animals - Male albino mice (ICR), supplied by Charles Rivers, Kingston, NY.

(2) Initial weight -- 22 to 30 grams.

(3) Quarantine -- Mice are held for a minimum of 7 days for evaluation of general health and physical condition.

(4) Acclimation -- All animals are held at the Medical Research and Evaluation Facility for at least 24 hours after quarantine prior to study initiation.

(5) Selection -- Animals selected for good physical condition based on appearance are entered in a computerized randomization procedure for assignment to a treatment group based on body weight. Group composition is structured to assure homogeneity of body weight across all dose groups.

(6) Animal Identification -- Animals will be uniquely identified using a numbered metal ear tag. Cage cards are color-coded by group.

(7) Housing -- Animals are housed individually in polycarbonate cages in stainless steel racks equipped with automatic watering systems.

(8) Lighting -- Fluorescent lighting, consisting of a light/dark cycle of 12 hours each per day.

(9) Temperature -- Maintained at 70 F ($\pm$5 F).

(10) Humidity -- Maintained at 50% ($\pm$10%).

(11) Diet -- Purina Certified Rodent Chow is available ad libitum during animal quarantine and treatment. No contaminants are known to be present in the feed which would interfere or affect the results of the study.

(12) Water Supply -- Water is supplied form the public water system and given ad libitum. No contaminants are known to be present in the water which would affect the results of the study.

B. Test Material

(1) HD is supplied by the USAMRDC/ICD. Purity, appropriate identification (batch number, lot number, state), and stability data are supplied by the USAMRDC/ICD. Purity and stability are confirmed periodically by Battelle for materiel stored at the Hazardous Materials Laboratory.

(2) Surety, security, and safety procedures for the use of HD are thoroughly outlined in facility plans, in personnel requirements for qualifications to work with agents, and in agent storage and use standard operating procedures. Specific procedures have been included in this document to ensure the safety of the personnel conducting this experiment.

C. Test Groups

(1) Range-Finding Study -- A range-finding study is conducted with 6 groups of 4 male mice each at doses between 15 and 50 mg/kg, bracketting the estimated LD_{50} (see table below). HD is

suspended in polyethylene glycol 200 (PEG 200) or other suitable carrier and administered subcutaneously to the dorsal surface of the back in a region mid-way between the shoulders and the rump. Mortality is observed after 72 hours.

Group No.	N	Dose (mg/kg)[a]
I	4	Vehicle control (PEG 200)
II	4	15.9
III	4	21.2
IV	4	28.2
V	4	37.6
VI	4	50.1

[a]Log Unit Interval = 0.1245

(2) Seven Day Lethality Study -- A 7-day LD_{50} for HD is determined from dose-response curves using male mice weighing 25-30 grams. Sufficient groups of 10 mice each are used to produce an LD_{50} with acceptable confidence intervals, with the initial dose selection based on the results of the range-finding study. The 7-day LD_{50} is replicated twice more and the composite LD_{50} calculated.

(3) The 30-day LD_{50} for HD is determined from dose-response curves using male mice weighing 25-30 grams. The animals are divided into 8 groups of 10 animals each, with Group I serving as the control and Groups II-VIII as the HD treatment groups. The doses are determined by careful analysis of the data from the range-finding and 7-day LD_{50} studies.

D. Application of Agent

(1) Each animal is injected subcutaneously (dorsal back skin) using a tuberculin or microliter syringe fitted with a 25- or 27-gauge needle. The volume for injection is based on body weight and is held constant for each dose group.

(2) Immediately after dosing, the injection site is decontaminated with 5% sodium hypochlorite.

(3) After decontamination, the animals are caged in groups according to dose and remain in the hood for ten minutes (or other suitable time period based on preliminary experimental data), after which time they are decontaminated a second time prior to being returned to the animal quarters and individually housed for the 3-, 7-, or 30-day observation period.

E. Collection of Blood Samples (30-Day Study Only)

(1) Peripheral blood samples are taken from the orbital sinus of two different mice of each group at 24, 48, 72, 96, and 120 hours after HD injection or until death of the entire group.

(2) Up to five additional blood samples may be taken during the study at the direction of the USAMRDC COTR and the concurrence of the MREF Manager.

(3) The selection of mice for blood sampling is made when animals are assigned to each treatment group during the pre-study randomization procedure.

(4) Blood is obtained from the orbital sinus using a glass capillary tube for the penetration and collection of the specimen. Slight pressure is applied to the site of penetration after sampling to prevent further blood loss.

(5) One blood smear per animal is prepared for each animal by quickly mixing 10 microliters of sampled blood with a drop of newborn calf serum on a microscope slide. The blood smear is air-dried and fixed in absolute methanol within one hour. Each slide is stained for 5 minutes with concentrated filtered Wright-Giemsa stain (prepared in phosphate buffer, pH 6.8, and aged at least one week). The stained slides are coded to permit scoring at 1000X (oil immersion) by an observer unaware of animal identity or treatment experience.

(6) The incidence of micronucleated cells among 500 polychromatic and 500 normochromatic erythrocytes is scored in the peripheral blood smear from each animal. Additionally, the polychromatic to normochromatic erythrocyte ratio is determined by noting the number of polychromatic cells in the fields containing the first 500 normochromatic cells.

(7) A blood sample from the orbital sinus will be used for determining the total and differential while blood cell counts at each interval for which a sample of blood is taken for micronuclei determination. Particular emphasis is placed on evaluating any transient leucopenia, leucocytosis, and/or agranulocytosis as a function of time and/or dose.

F. Observations (30-Day Study Only)

(1) All mice are observed twice daily (AM/PM) for the duration of the test period (or until death) for signs of clinical abnormality.

(2) The incidence of mortality and elapsed time to death (if death observed) or date and time found dead are recorded.

(3) Qualitative assessment of food and water utilization is to be noted.

(4) Individual body weights are obtained on Monday, Wednesday, and Friday of each study week for surviving animals from Day 1 through Day 30.

(5) Surviving animals are euthanized after the scheduled termination of the study.

G. Decontamination

Immediately following the subcutaneous injection of HD, the injection site is decontaminated with 5% sodium hypochlorite. Each mouse remains in the hood for ten minutes (or other suitable time period based on preliminary experimental data) before being decontaminated a second time prior to being removed for subsequent evaluations.

H. Specific Procedures

(1) Exposure and decontamination is controlled by one investigator who also maintains the laboratory notebook. A second investigator prepares the materials and delivers them to a third, operating investigator in proper sequence and timing. The third operating investigator applies the agent and performs decontaminating procedures while wearing approved protective gloves and an apron. A fourth investigator maintains a supply

of mice from the preparation area to the exposure hoods and reports signs of toxicity or death of dosed mice to the reporting investigator.

(2) All animals are inspected after the agent has been applied to the last animal. Animals are observed for signs of toxicity after dosing until the end of the workday and twice daily until death or until the test period is completed.

7. Necropsy and Histopathology:

Gross post-mortem examinations will not be performed for any animals during the study. No tissue samples are to be saved and all animal carcasses are to be discarded.

8. Records to be Maintained:

A. CSM accountability log and inventory

B. Preparation of reagents and dosage administration

C. Animal data

D. Mortality

e. Clinical observations and evaluations

F. Decontamination monitoring and disposal records

9. Statistical Methods:

An LD_{50} calculation, slope, and 95% confidence interval are made based on the results of the 30-day survival data. The calculation is performed according to the probit procedure of Finney, Probit Analyses, 3rd Edition (1971), or by other suitable techniques.

10. Reports:

A final report is prepared and submitted within 28 calendar days after completion of the task. It includes at least the following:

1. Signature page for key study individuals and their responsibilities
2. Experimental design
3. Animal supplier

4. Test animal selection criteria
5. Test material description and preparation
6. Application procedures
7. Description of clinical observations
8. Tabulation of response data by dose
9. Statistical methodology used
10. Discussion
11. Photographs

11. Approval Signatures:

Study Director	2/15/85 Date
Chief Veterinarian	2-19-85 Date
USAMRDC Monitor	20 Feb 85 Date
USAMRDC Principal Investigator	2 July 85 Date

Evaluation of Potential Therapeutic Effects of Inhibitors Against Mustard in Mice

Study Performed by Battelle Columbus Laboratories,
505 King Avenue, Columbus, Ohio 43201

1. Study Director: Ronald L. Joiner, Ph.D.

2. Veterinarian: H. Hugh Harroff, Jr., D.V.M.

3. Sponsor: U.S. Army Medical Research and Development Command

4. Sponsor Monitor: LTC Howard Johnson, USAMRICD

5. Objective:

The objective of the study is to determine the therapeutic efficacy of nicotinamide, 3-aminobenzamide, and nicotinic acid in reducing the toxicity arising from the subcutaneous administration of HD in the laboratory mouse. A defined dose of HD (e.g. LD20, LD50, LD80) is given to determine the efficacy of administering nicotinamide, 3-aminobenzamide, or nicotinic acid through single and multidose regimens.

6. Experimental Design:

A. Test System

(1) Animals - Male albino mice (ICR), supplied by Charles Rivers, Kingston, NY.

(2) Initial weight -- 22 to 25 grams.

(3) Quarantine -- Mice are held for a minimum of 7 days for evaluation of general health and physical condition.

(4) Acclimation -- All animals are held at the Medical Research and Evaluation Facility for at least 24 hours after quarantine prior to study initiation.

(5) Selection -- Animals selected for good physical condition based on appearance are entered in a computerized randomization procedure for assignment to a treatment group based on body

weight. Group composition is structured to assure homogeneity of body weight across all dose groups.

(6) Animal Identification -- Animals will be uniquely identified using a numbered metal ear tag. Cage cards are color-coded by group.

(7) Housing -- Animals are housed individually in polycarbonate cages in stainless steel racks equipped with automatic watering systems.

(8) Lighting -- Fluorescent lighting, consisting of a light/dark cycle of 12 hours each per day.

(9) Temperature -- Maintained at 70 F ($\pm$5 F).

(10) Humidity -- Maintained at 50% ($\pm$10%).

(11) Diet -- Purina Certified Rodent Chow is available ad libitum during animal quarantine and treatment. No contaminants are known to be present in the feed which would interfere or affect the results of the study.

(12) Water Supply -- Water is supplied from the public water system and given ad libitum. No contaminants are known to be present in the water which would affect the results of the study.

B. Test Material

(1) HD is supplied by the USAMRDC/ICD. Purity, appropriate identification (batch number, lot number, state), and stability data are supplied by the USAMRDC/ICD. Purity and stability are confirmed periodically by Battelle for materiel stored at the Hazardous Materials Laboratory.

(2) Nicotinamide, 3-aminobenzamide, and nicotinic acid are purchased from a commercial source.

(3) Surety, security, and safety procedures for the use of HD are thoroughly outlined in facility plans, in personnel requirements for qualifications to work with agents, and in agent storage and use standard operating procedures. Specific procedures have been included in this document to ensure the safety of the personnel conducting this experiment.

C. Test Groups

Nicotinamide, 3-aminobenzamide, and nicotinic acid are evaluated separately in male albino mice to determine their therapeutic efficacy as inhibitors of toxicity arising from subcutaneous exposure to HD at a defined dose. Inhibitors are administered using a single or multiple dose regimen and evaluated for evidence of a protective effect from HD toxicity.

(1) Each of the 11 groups indicated below contains 10 males for evaluation of each of the inhibitors listed for three separate doses of HD.

(2) Two experimental trials per dose of HD are performed.

(3) Clinical appearance, mortality, body weight, hematology, and histopathology will serve as experimental endpoints.

Groups

Group 1	Vehicle control (PEG 200 sc., saline pH 7.4 ip)
Group 2	Low Level Inhibitor only, no HD (saline sc, inhibitor ip)
Group 3	High Level Inhibitor only, no HD (saline sc, inhibitor ip)
Group 4	HD only, no inhibitor (HD sc, saline ip)
Group 5	Low Level Inhibitor (ip) given 1 hour before HD injection (sc)
Group 6	High Level Inhibitor (ip) given 1 hour before HD injection (sc)
Group 7	Low Level Inhibitor (ip) given 1 hour after HD injection (sc)
Group 8	High Level Inhibitor (ip) given 1 hour after HD injection (sc)
Group 9[a]	Low Level Inhibitor (ip) given 1 hour and 4 hours after HD injection (sc)
Group 10[a]	High Level Inhibitor (ip) given 1 hour and 4 hours after HD injection (sc)
Group 11[a]	Multi-level Inhibitor (ip) given 1 hour before and 1 hour and 4 hours after HD injection (sc)

[a] Indicates multiple dose regimen

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Inhibitors

Nicotinamide (mg/kg)		3-Aminobenzamide (mg/kg)	Nicotinic acid (mg/kg)
High	500	500	500
Low	100	100	50
Multi-level	100[b]	200[b]	150[b]

(b) Multiple dose for Groups 9, 10, and 11

D. Application of Agent

(1) Animals designated for treatment are injected subcutaneously (dorsal back skin) with a defined dose of HD using a tuberculin or microliter syringe fitted with a 25- or 27-gauge needle.

(2) All solutions of HD use polyethylene glycol 200 (PEG 200) or other suitable carrier as the vehicle for injection.

(3) The volume for injection is based on body weight and is held constant for each group.

(4) Immediately after dosing of HD, the injection site is decontaminated with 5% sodium hypochlorite.

(5) After decontamination, the animals are held in the approved dosing hood for 10 minutes (or other suitable time period based on preliminary experimental data) before being decontaminated a second time prior to being removed to the animal rooms for further observations.

E. Application of Inhibitors

(1) At the scheduled time, the inhibitor is given by intraperitoneal injection using a tuberculin syringe fitted with a 25- or 27-gauge needle.

(2) The volume for injection is based on body weight and is held constant for each group.

(3) Nicotinamide, 3-aminobenzamide, or nicotinic acid for injection is prepared in sterile saline (U.S.P.) with the pH adjusted to 7.4 with 0.1 N NaOH.

F. Collection of Blood Samples

(1) Peripheral blood samples are taken from the orbital sinus of two different mice of each group at 24, 48, 72, 96, and 120 hours after HD injection or until death of the entire group.

(2) Up to five additional blood samples may be taken during the study at the direction of the USAMRDC COTR and the concurrence of the MREF Manager.

(3) The selection of mice for blood sampling is made when animals are assigned to each treatment group during the pre-study randomization procedure.

(4) Blood is obtained from the orbital sinus using a glass capillary tube for penetration and collection of the specimen. Slight pressure is applied to the site of penetration after sampling to prevent further blood loss.

(5) One blood smear per animal (separate slides) is prepared for each animal by quickly mixing 10 microliters of sampled blood with a drop of newborn calf serum on a microscope slide. The blood smear is air-dried and fixed in absolute methanol within one hour. Each slide is stained for 5 minutes with concentrated filtered Wright-Giemsa stain (prepared in phosphate buffer, pH 6.8, and aged at least one week). The stained slides are coded to permit scoring at 1000X (oil immersion) by an observer unaware of the animal identity or treatment experience.

(6) The incidence of micronucleated cells among 500 polychromatic and 500 normochromatic erythrocytes is scored in the peripheral blood smear from each animal. Additionally, the polychromatic to normochromatic erythrocyte ratio is determined by noting the number of polychromatic cells in the fields containing the first 500 normochromatic cells.

(7) A blood sample from the orbital sinus will be used for determining the total and differential white blood cell counts at each time interval for which a sample of blood is taken for micronuclei determination. Particular emphasis is placed on evaluating any transient leucopenia, leucocytosis, and/or agranulocytosis as a function of time and/or dose.

Revised November 12, 1984

G. Observations

(1) All mice are observed twice daily (AM/PM) for the duration of the test period (or until death) for signs of clinical abnormality.

(2) The incidence of mortality and elapsed time to death (if death observed) or date and time found are recorded.

(3) Qualitative assessment of food and water utilization are noted.

(4) Procedures for disposition of early death animals are indicated in the necropsy section.

(5) Individual body weights are obtained on Monday, Wednesday, and Friday of each study week for surviving animals from Day 1 through Day 30.

(6) In animals surviving to the scheduled termination of the study (Day 30), blood is obtained at terminal sacrifice for the following tests: hemoglobin concentration, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, neutrophils (segmented and non-segmented), lymphocytes, monocytes, eosinophils, basophils, and reticulocytes. Blood is obtained from the orbital sinus.

H. Decontamination

Immediately following the subcutaneous injection of HD, the injection site is decontaminated with 5% sodium hypochlorite. Each mouse remains in the hood for ten minutes (or other suitable time period based on preliminary experimental data) before being decontaminated a second time prior to being removed for subsequent evaluations.

7. <u>Necropsy and Histopathology</u>:

A. Necropsy

(1) A complete necropsy is performed on all early deaths and on three animals randomly selected at the time of the pre-study randomization procedure from each of the groups surviving to the scheduled termination of the study. The remaining survivors are euthanized without further examination. Animals that die

outside the normally scheduled work day or on weekends are dissected and 10% formalin injected into the intestines and other organs, and the whole animal placed in formalin. The animals ear with ear tag accompanies the tissue through processing.

(2) The selection of animals for necropsy is based on the sequential order in which each animal was assigned to treatment within a dose group during the pre-study randomization. The first three animals selected by the computer for each dose group are designated as the initial candidates for necropsy at the scheduled termination of the study. In the event of early death in the candidate animals, the next animal in sequence for the affected group is selected.

B. Histopathology

The following tissues are harvested at the time of necropsy for microscopic pathology.

(1) Skin in the area of the HD injection site
(2) Bone marrow (sternum and femur, decalcified sections)
(3) Liver
(4) Spleen
(5) Small intestine
(6) Large intestine
(7) Thymus-like tissue present
(8) Mandibular and mesenteric lymph nodes
(9) Abnormal tissue identified at necropsy

8. <u>Records to be Maintained</u>:

A. CSM accountability log and inventory

B. Preparation of reagents and dosage administration

C. Animal data

D. Mortality

E. Clinical observations and evaluations

F. Decontamination monitoring and disposal records

9. Statistical Methods:

To be supplied by the USAMRDC.

10. Reports:

A final report is prepared and submitted within 28 calendar days after completion of the task. It includes at least the following:

1. Signature page for key study individuals and their responsibilities
2. Experimental design
3. Animal supplier
4. Test animal selection criteria
5. Test material description and preparation
6. Application procedures
7. Description of clinical observations
8. Tabulation of response data by dose
9. Statistical methodology used
10. Discussion
11. Photographs

11. Approval Signatures:

Ronald [signature] 2/15/85
Study Director — Date

H. Hugh Harroff, Jr. DVM 2-19-85
Chief Veterinarian — Date

Howard R. Johnson 20 Feb 85
USAMRDC Monitor — Date

Floyd B. Buckley 2 July 85
USAMRDC Principal Investigator — Date

Revised November 12, 1984

12. <u>Amendment A - September 6, 1985:</u>

This is to document changes in Protocol 19 (Evaluation of Potential Therapeutic Effects of Inhibitors Against Mustard in Mice).

1. <u>Page 3, Section 6.C.</u>

   The test groups are redefined as follows with the order indicative of the dosing sequence:

   Group A: Vehicle Control (Ethanol, S.C.); (Saline, i.p. at 1 hour before)
   Group B: Low Level Inhibitor only, no HD (Ethanol, S.C.); (inhibitor, i.p., at 1 hour before)
   Group C: High Level Inhibitor only, no HD (Ethanol, S.C.); (inhibitor, i.p., at 1 hour before)
   Group D: High Level Inhibitor (i.p.) given 1 hour and 4 hours after HD injection (S.C.)
   Group E: Low Level Inhibitor (i.p.) given 1 hour and 4 hours after HD injection (S.C.)
   Group F: Multi-Level Inhibitor (i.p.) given 1 hour before and 1 hour and 4 hours after HD injection (S.C.)
   Group G: High Level Inhibitor (i.p.) given 1 hour before the HD injection (S.C.)
   Group H: Low Level Inhibitor (i.p.) given 1 hour after the " injection (S.C.)
   Group I: High Level Inhibitor (i.p.) given 1 hour after the HD injection (S.C.)
   Group J: Low Level Inhibitor (i.p.) given 1 hour before the HD injection (S.C.)
   Group K: HD only, no inhibitor (HD, S.C.); (Saline, i.p. at 1 hour before)

2. <u>Page 4, Section 6.C. footnote (b) is replaced with the following:</u>

   (b) Multiple dose for Group 11

3. <u>Page 4, Section 6.D.(2) is replaced with the following:</u>

   All solutions of HD are reagent grade (200 proof) ethanol as the vehicle for injection.

4. Page 4, Section 6.D.(3) is replaced with the following:

   The volume for injection is based on body weight at 25 µl per 30 g. Control animals receive the same volume as the heaviest animal among the test groups.

5. Page 4, Section 6.E.(2) is replaced with the following:

   The volume for injection is based on body weight at 100 µl per 10 g. Control animals receive the same volume as the heaviest animal among the test groups.

6. Page 5, Section 6.F.(4):

   Replace "glass capillary tube" with "22 gauge 1-inch disposable needle."

7. Page 6, Section 6.G.(3):

   Remove.

8. Page 6, Section 6.H. is replaced with the following:

   Immediately following the subcutaneous injection of HD, the injection site is decontaminated with 5 percent sodium hypochlorite solution followed by two distilled water rinses. Each mouse remains in the hood for ten minutes (or other suitable time period based on preliminary experimental data) before being decontaminated and double-rinsed a second time prior to being removed for subsequent evaluations.

9. Page 7, Section 7.B.:

   Replace "necropsy" with "scheduled necropsy." Amend with "A Final Report that addresses the review comments of the USAMRDC is prepared and submitted within 30 working days of receipt of comments".

10. Page 8, Section 10:

    Replace "final report" with "draft final report."

13. Approval Signatures:

Ronald B. Joiner — September 9, 1985
Ronald L. Joiner
Study Director
Date

H. Hugh Harroff, Jr. DVM — September 10, 1985
H. Hugh Harroff, Jr.
Chief Veterinarian
Date

Howard C. Johnson — 16 Sep 85
LTC(P) Howard C. Johnson
USAMRDC Monitor
Date

Floyd B. Brinkley — 16 Sept 85
Floyd B. Brinkley
USAMRDC Principal Investigator
Date

14. Amendment B - September 27, 1985:

This is to document changes in Protocol 19 (Evaluation of Potential Therapeutic Effects of Inhibitors Against Mustard in Mice).

1. Page 3, Section 6.C.(1) is replaced with the following:

   Each of the 11 groups indicated below (with the exception of Group K, which replaces the name for Group 4 - see Amendment A) contains 10 males for evaluation of each of the inhibitors listed for three separate dose levels of HD. Group K is assigned either 10 animals for all experiments using nicotinamide as the inhibitor or 30 animals for all experiments using nicotinic acid or 3-aminobenzamide as the inhibitor.

2. Page 4, Section 6.E.(3) is replaced with the following:

   Nicotinamide, 3-aminobenzamide, or nicotinic acid for injection is prepared in sterile saline (U.S.P.) with the pH adjusted to 7.4. The pH adjustments are made using 10N, 1N, and/or 0.1N NaOH solutions in order to minimize concentration changes.

3. Amendment A, Page 11, Section 6.D.(3) is replaced with the following:

   Each HD dilution is verified analytically by gas chromatography. The dose volume per animal is adjusted so that the analytically determined HD dose is delivered as required (LD20, LD50, or LD80).

15. Approval Signatures for Amendment B:

Ronald L. Joiner
Ronald L. Joiner, Ph.D.
Study Director

1 October 1985
Date

H. Hugh Harroff, Jr. D.V.M.
H. Hugh Harroff, Jr., D.V.M.
Chief Veterinarian

2 October 1985
Date

Howard C. Johnson
LTC(P) Howard C. Johnson, D.V.M.
USAMRDC/ICD Monitor

5 Nov 85
Date

Floyd B. Brinkley
Floyd B. Brinkley
USAMRDC Principal Investigator

25 October 1985
Date

16. Amendment C - January 10, 1986:

This is to document changes in Protocol 19 (Evaluation of Potential Therapeutic Effects of Inhibitors Against Mustard in Mice).

Page 4, Section 6.E.(2) is replaced with the following:

The volume for inhibitor solution injection is based on body weight. Nicotinamide and nicotinic acid solutions are administered at 100 µl per 10 g of body weight. Three-amino benzamide solution is administered at 300 µl per 10 g of body weight, due to solubility limitations of 3-amino benzamide in normal saline. Control animals receive the same volumes as the heaviest animal among the test groups.

17. Approval Signatures for Amendment C:

Ronald L. Joyner
Ronald L. Joyner, Ph.D.
Study Director

14 January 1986
Date

H. Hugh Harroff, Jr. DVM
H. Hugh Harroff, Jr., D.V.M.
Chief Veterinarian

14 January 1986
Date

Howard C. Johnson
LTC(P) Howard C. Johnson, D.V.M.
USAMRDC/ICD Monitor

3 Jan 86
Date

Floyd B. Brinkley
Floyd B. Brinkley
USAMRDC Principal Investigator

19 Feb 86
Date

APPENDIX B

Figures

FIGURE 2.1. IDENTIFICATION OF THE TREATMENT GROUPS IN THE INHIBITOR STUDIES BY LETTER DESIGNATION

Agent	Saline	Inhibitor Level									No. Applic. of Inhibitor
		Low Level			High Level			Multilevel			
		-1 hr	+1 hr	+4 hr	-1 hr	+1 hr	+4 hr	-1 hr	+1 hr	+4 hr	
none	A										0
none		B			C						1
HD	K										0
HD		J	H		G	I					1
HD			E			D					2
HD								F			3

Amount of inhibitor per dose:	Low Level	High Level	Multilevel
NIC	100 mg/kg	500 mg/kg	100 mg/kg
3AB	100	500	200
NA	50	500	150

NIC = Nicotinamide
3AB = 3-Aminobenzamide
NA = Nicotinic Acid

FIGURE 2.2. AGGREGATION OF PROXIMAL DOSES IN MREF PROTOCOL 18 FOR FORMATION OF HEMATOLOGY GROUP SETS

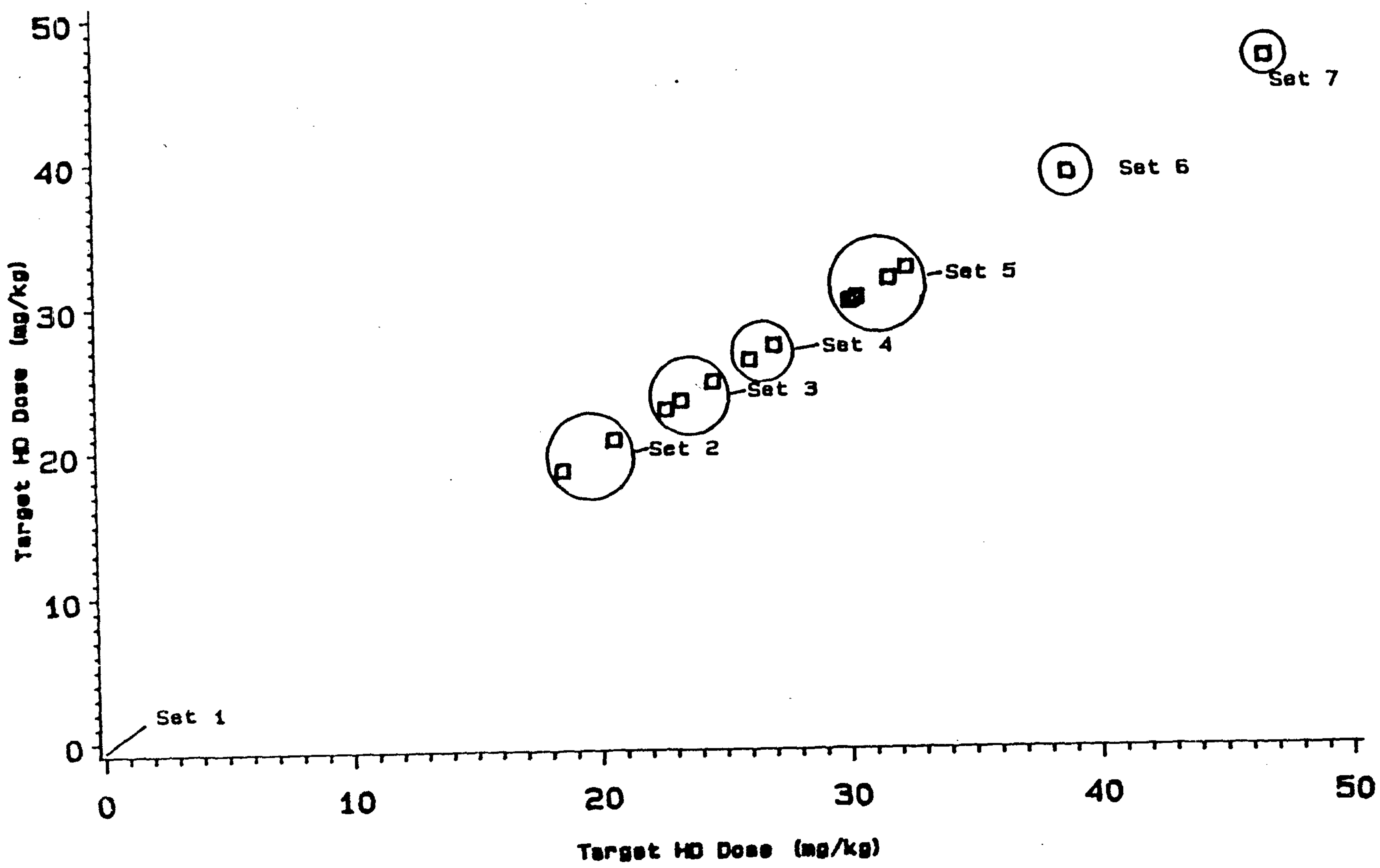


FIGURE 3.1. 14-DAY COMPOSITE PROBIT ANALYSIS PLOT FOR DILUTE HD ADMINISTERED SUBCUTANEOUSLY IN MICE

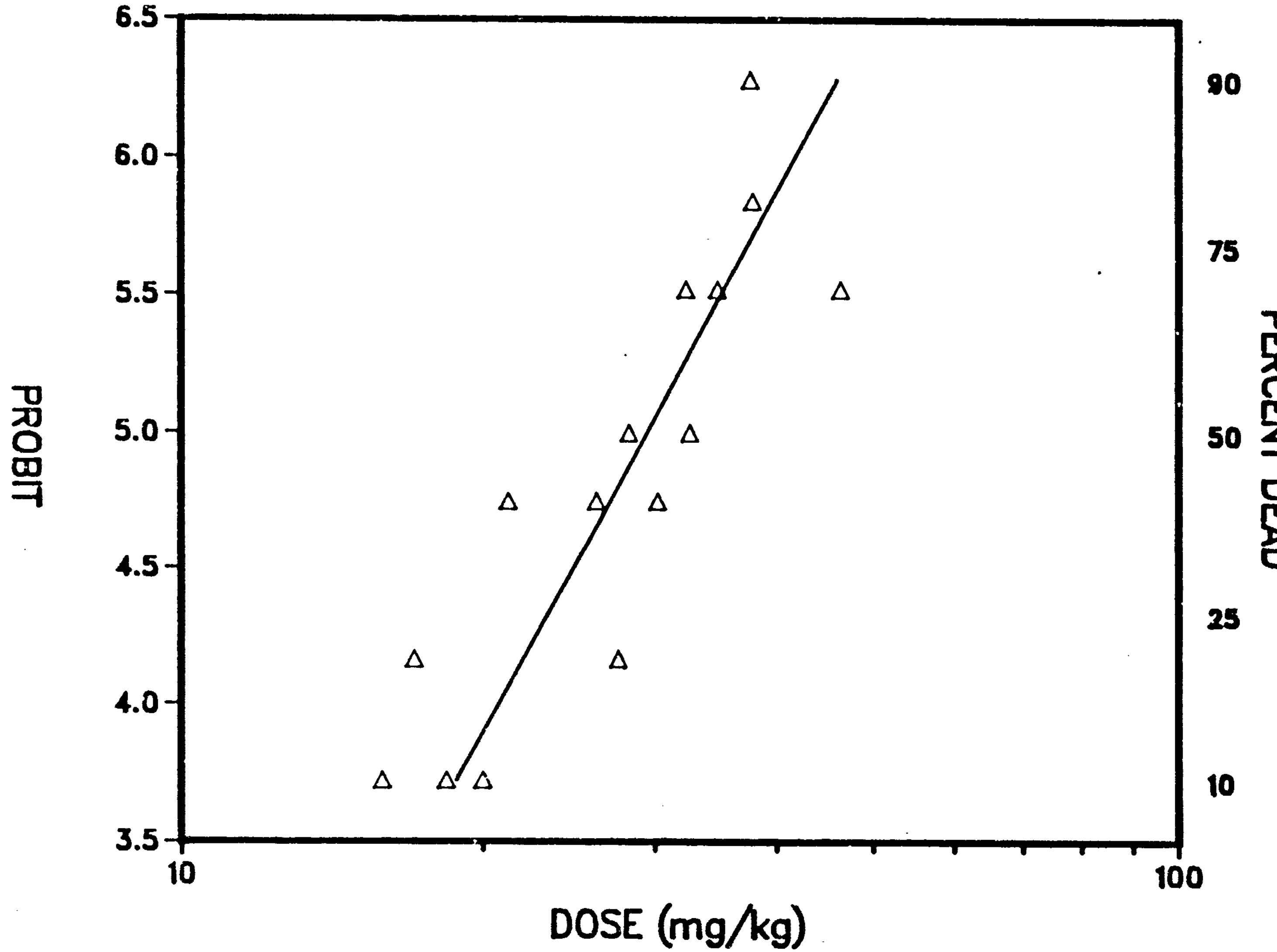


FIGURE 3.2. 30-DAY COMPOSITE PROBIT ANALYSIS PLOT FOR DILUTE HD ADMINISTERED SUBCUTANEOUSLY IN MICE

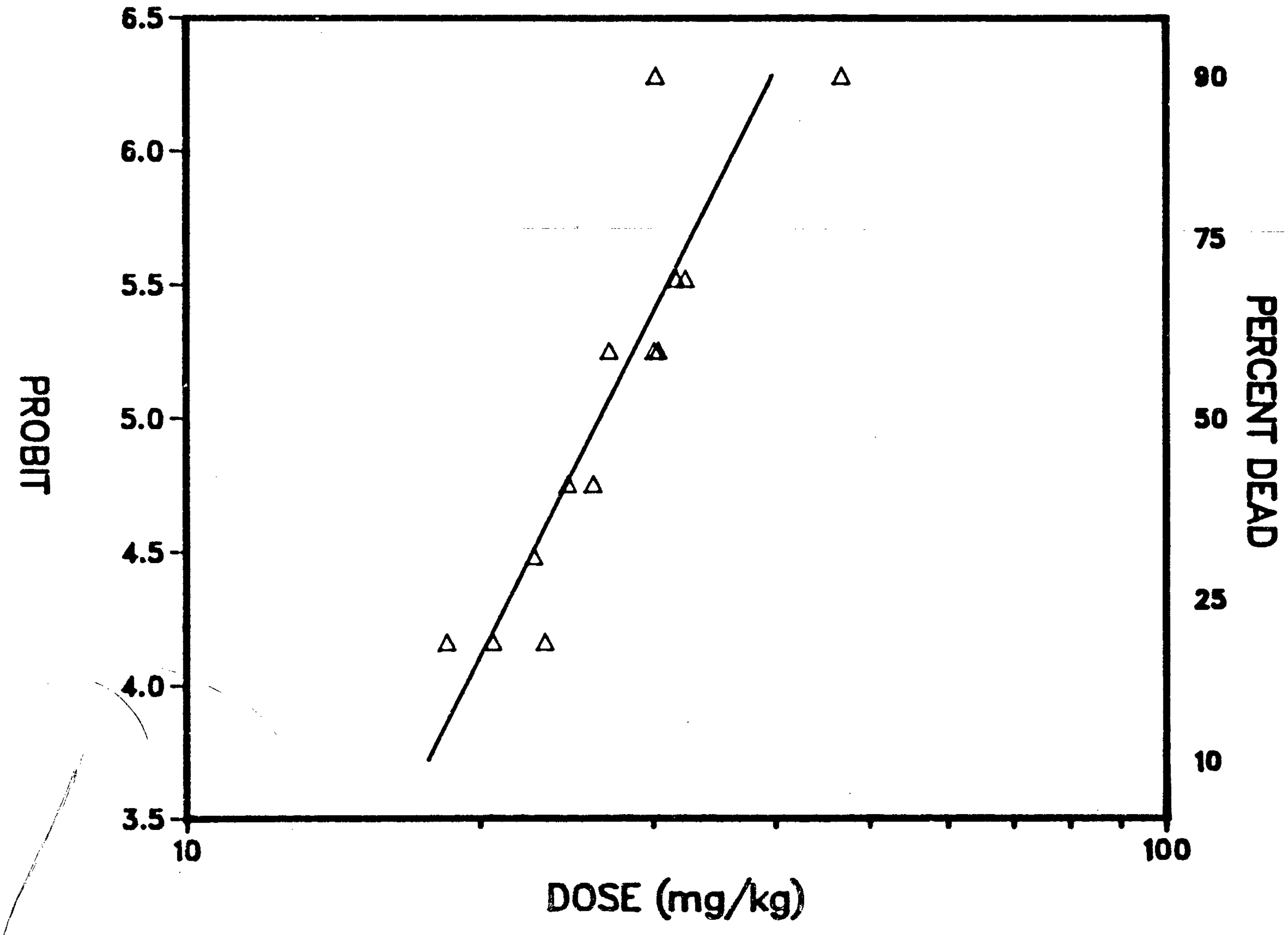


FIGURE 3.3. PROBIT ANALYSIS COMPOSITE PLOT FOR LETHALITIES RECORDED FOR 7 DAYS FOLLOWING ADMINISTRATION OF DILUTE HD SUBCUTANEOUSLY IN MICE

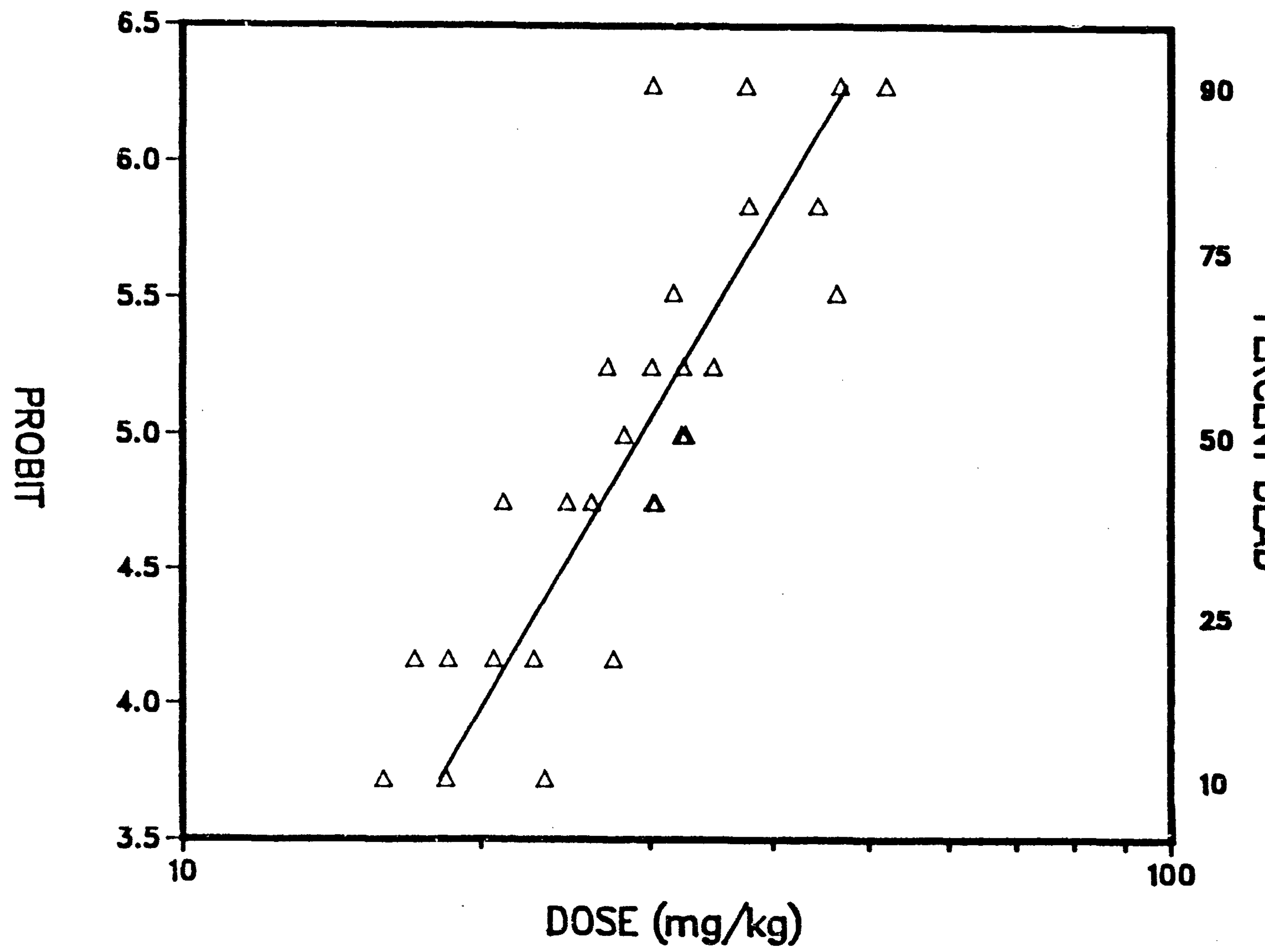


FIGURE 3.4. PROBIT ANALYSIS COMPOSITE PLOT FOR LETHALITIES RECORDED FOR 14 DAYS FOLLOWING ADMINISTRATION OF DILUTE HD SUBCUTANEOUSLY IN MICE

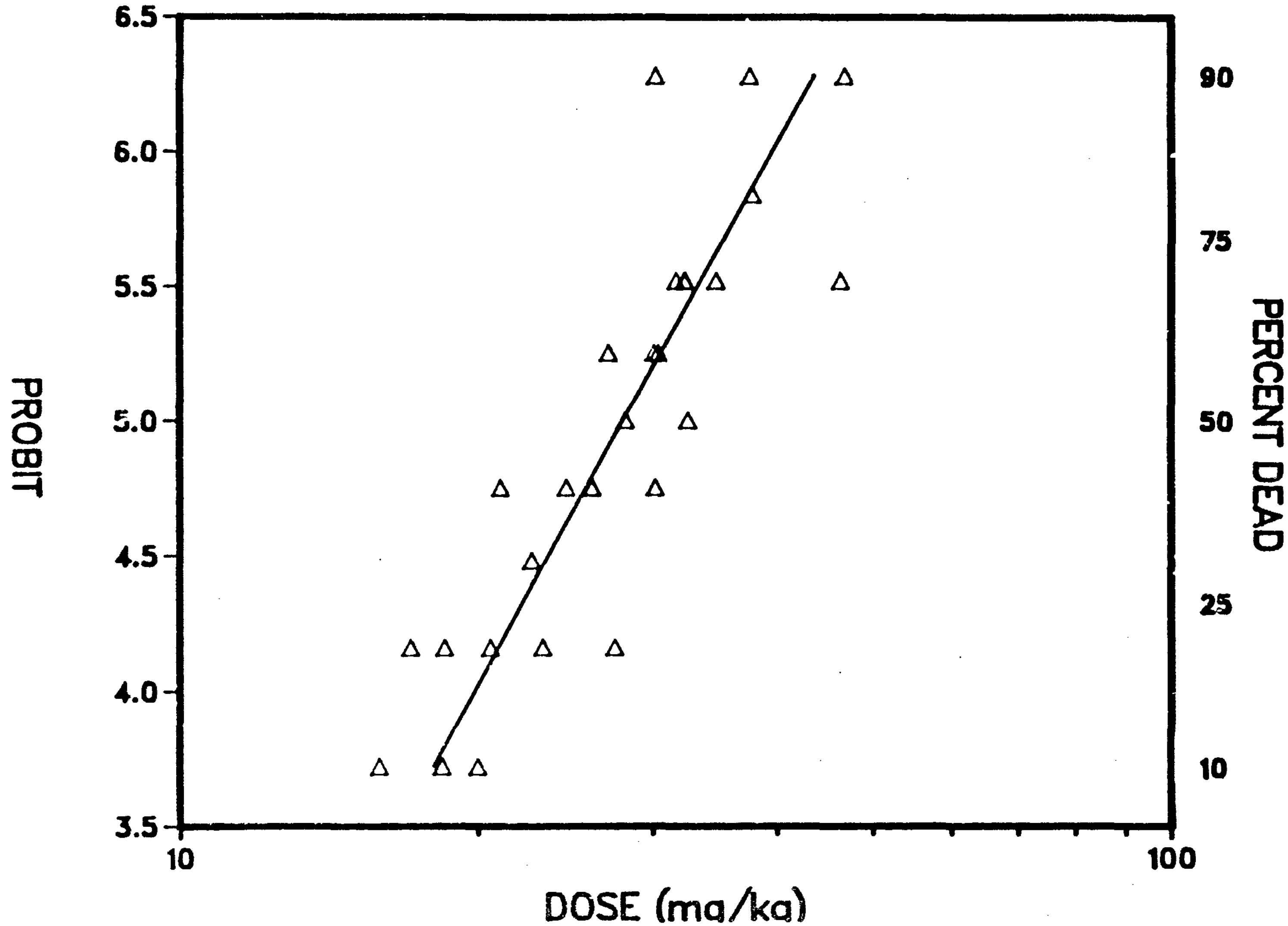


FIGURE 3.5. MOUSE HEMATOLOGIC RESPONSE TO 6 HD DOSE RANGES
VERSUS TIME - MEAN WHITE CELL COUNT

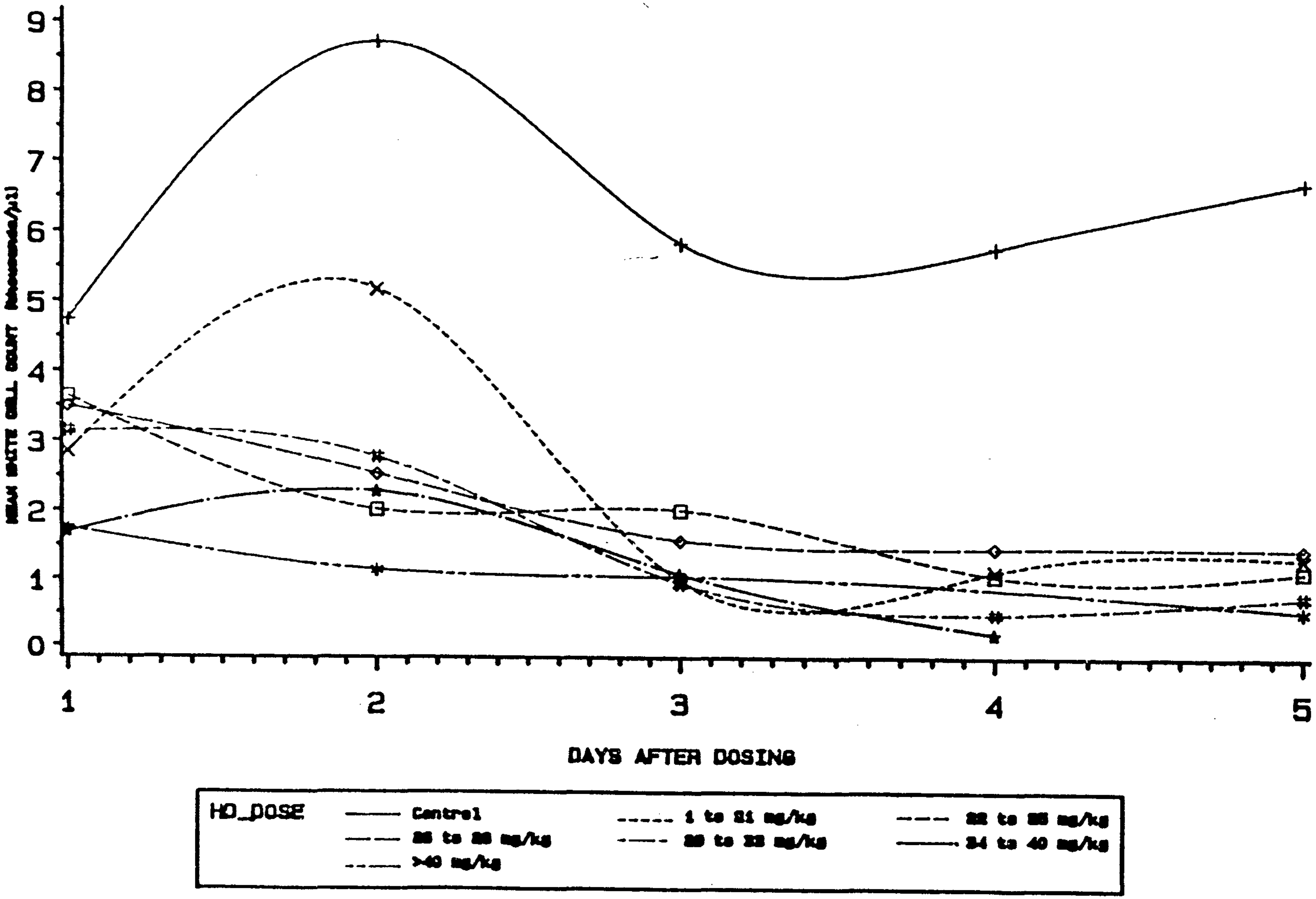


FIGURE 3.6. MOUSE HEMATOLOGIC RESPONSE TO 6 HD DOSE RANGES VERSUS TIME - MEAN LYMPHOCYTE COUNT

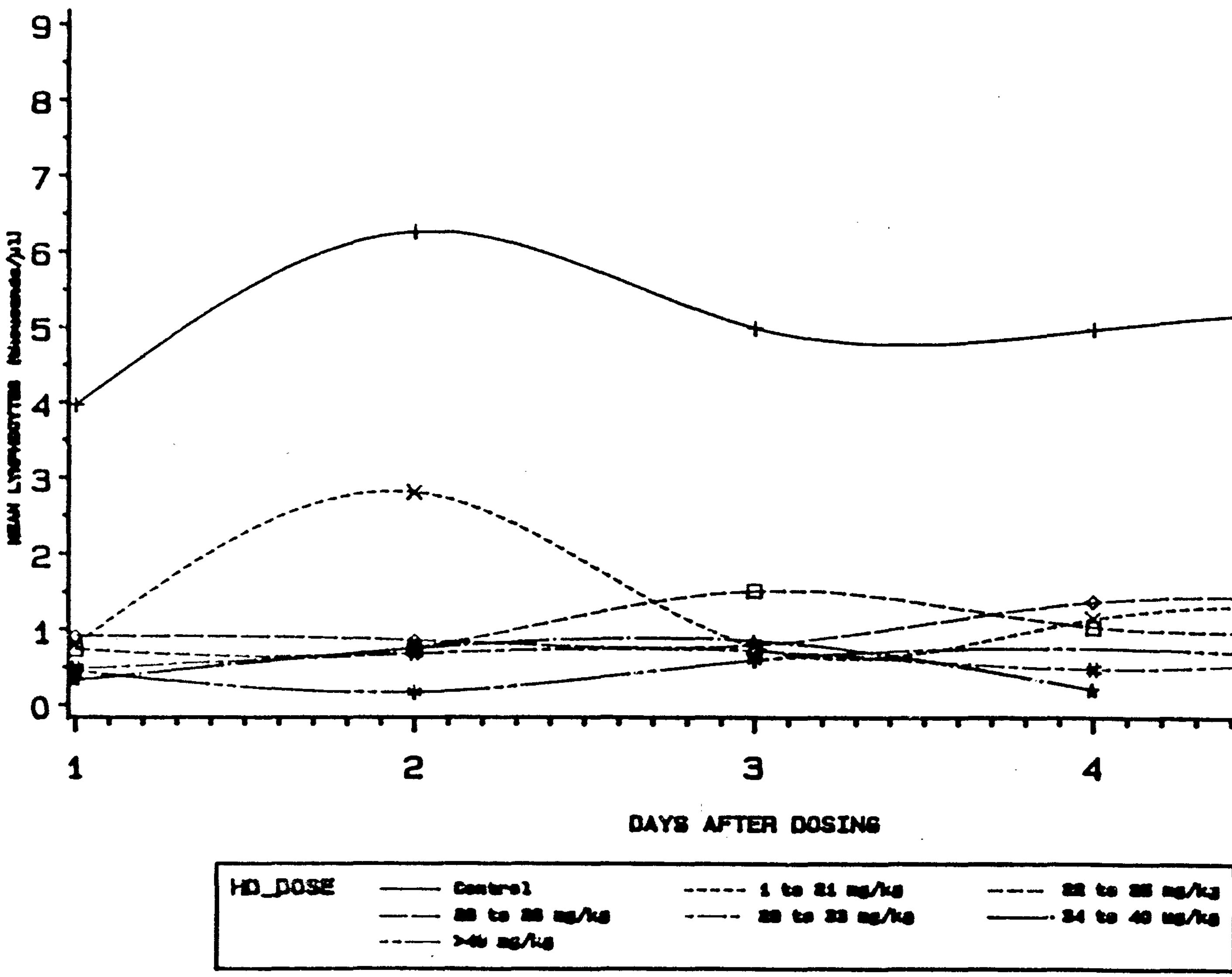


FIGURE 3.7. MOUSE HEMATOLOGIC RESPONSE TO 6 HD DOSE RANGES VERSUS TIME - MEAN SEGMENTED NEUTROPHIL COUNT

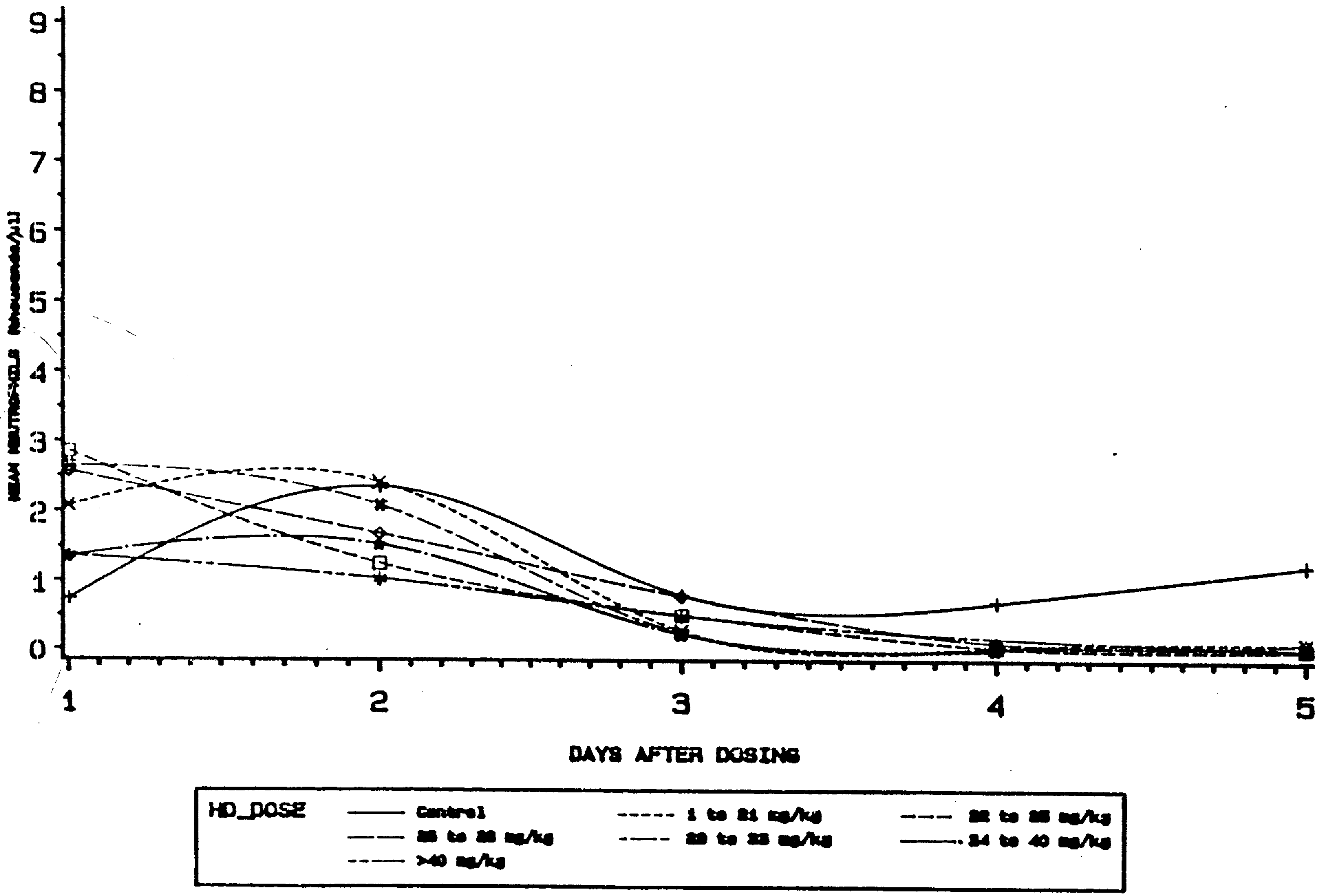


FIGURE 3.8. MOUSE HEMATOLOGIC RESPONSE TO 6 HD DOSE RANGES VERSUS TIME - MEAN MICRONUCLEATED RBC (PER 500 NORMOCHROMATIC RBC)

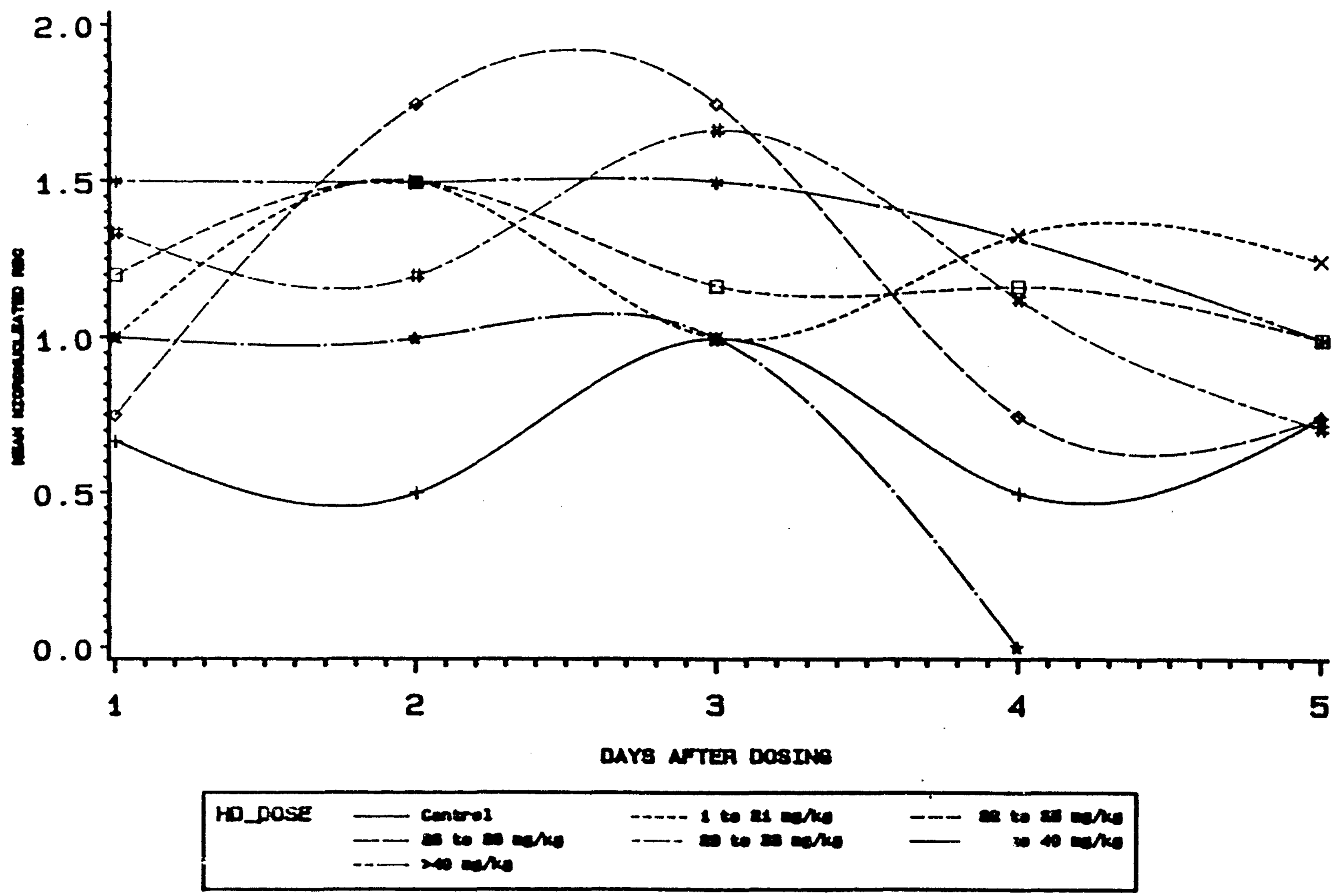


FIGURE 3.9. MOUSE HEMATOLOGIC RESPONSE TO 6 HD DOSE RANGES VERSUS TIME - MEAN MICRONUCLEATED RBC (PER 500 POLYCHROMATIC RBC)

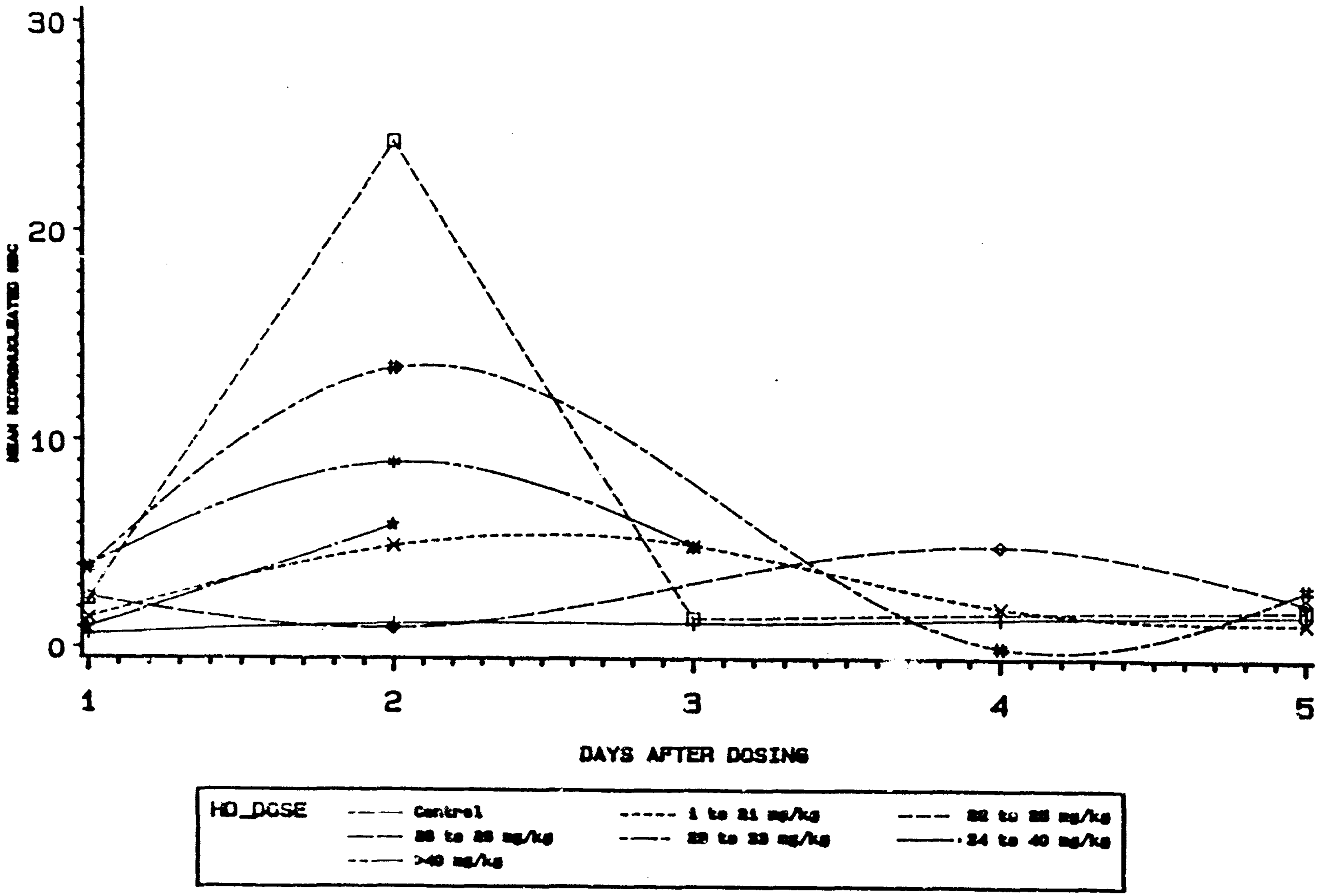


FIGURE 3.10. DAILY PERCENT MORTALITY CORRELATED WITH WHITE CELL COUNT IN MICE DOSED WITH HD AT 26 TO 28 mg/kg RANGE

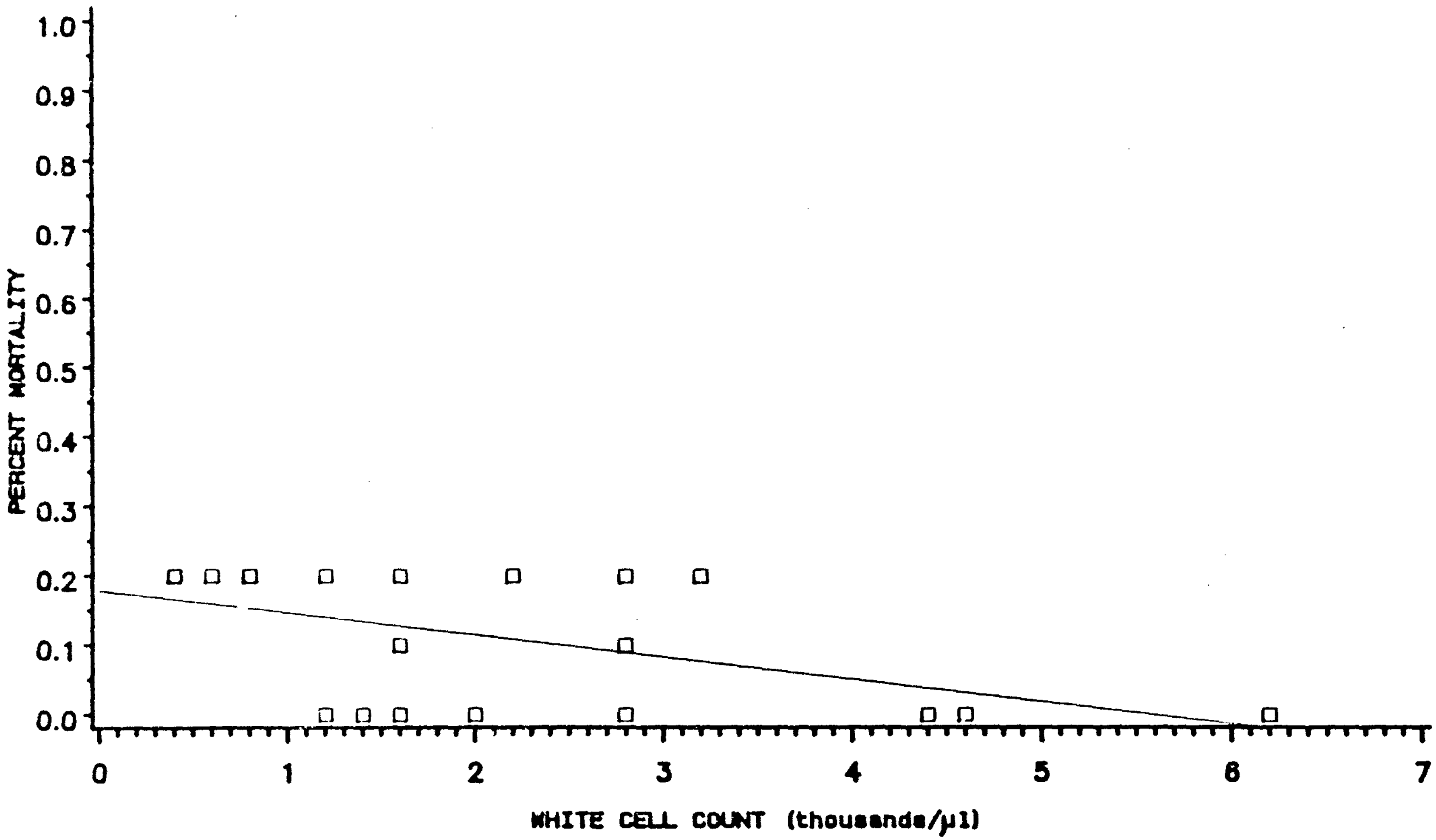


FIGURE 3.11. DAILY PERCENT MORTALITY CORRELATED WITH WHITE CELL COUNT IN MICE DOSED WITH HD AT 29 TO 33 mg/kg RANGE

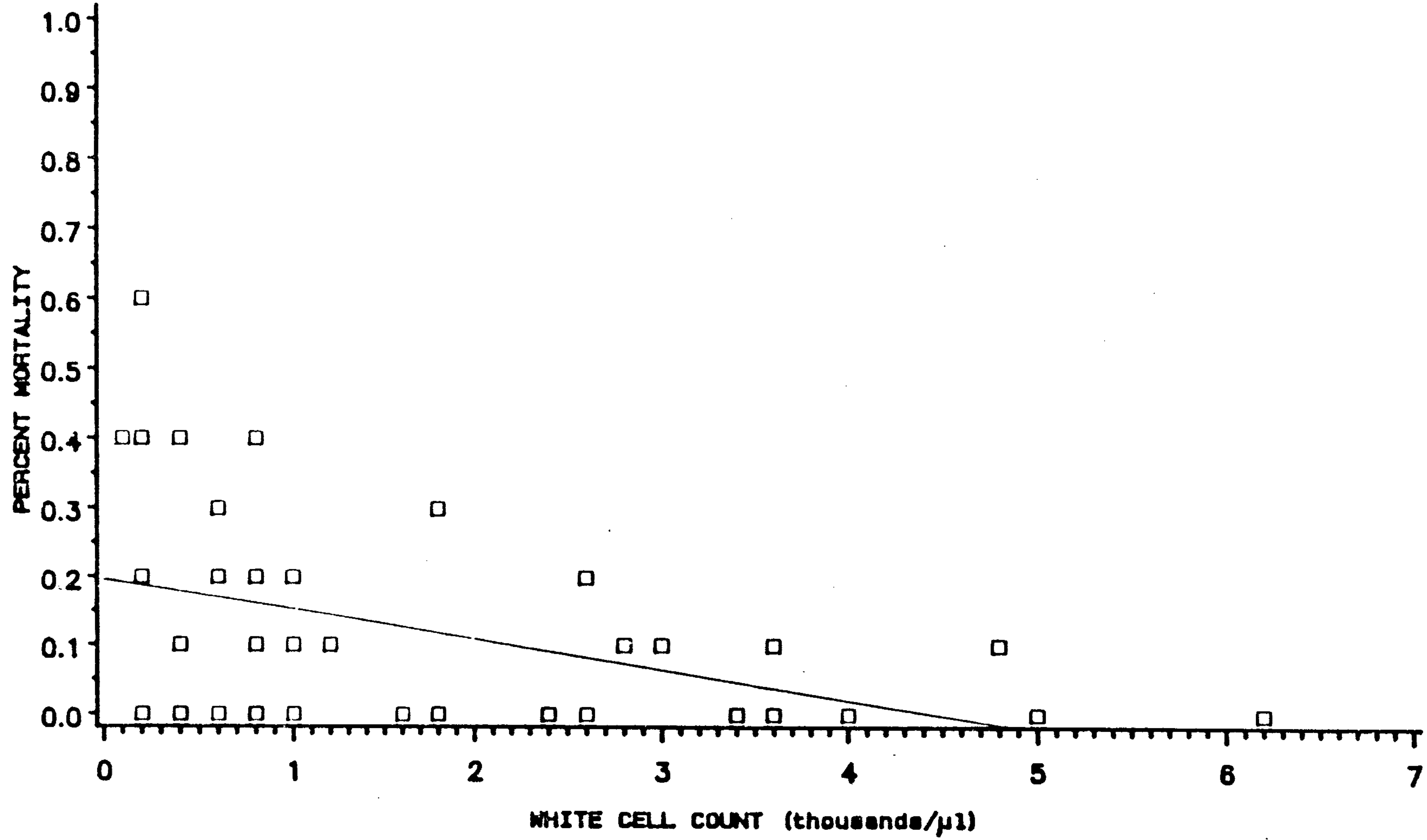


FIGURE 3.12. DAILY PERCENT MORTALITY CORRELATED WITH SEGMENTED NEUTROPHIL COUNT IN MICE DOSED WITH HD AT 22 TO 25 mg/kg RANGE

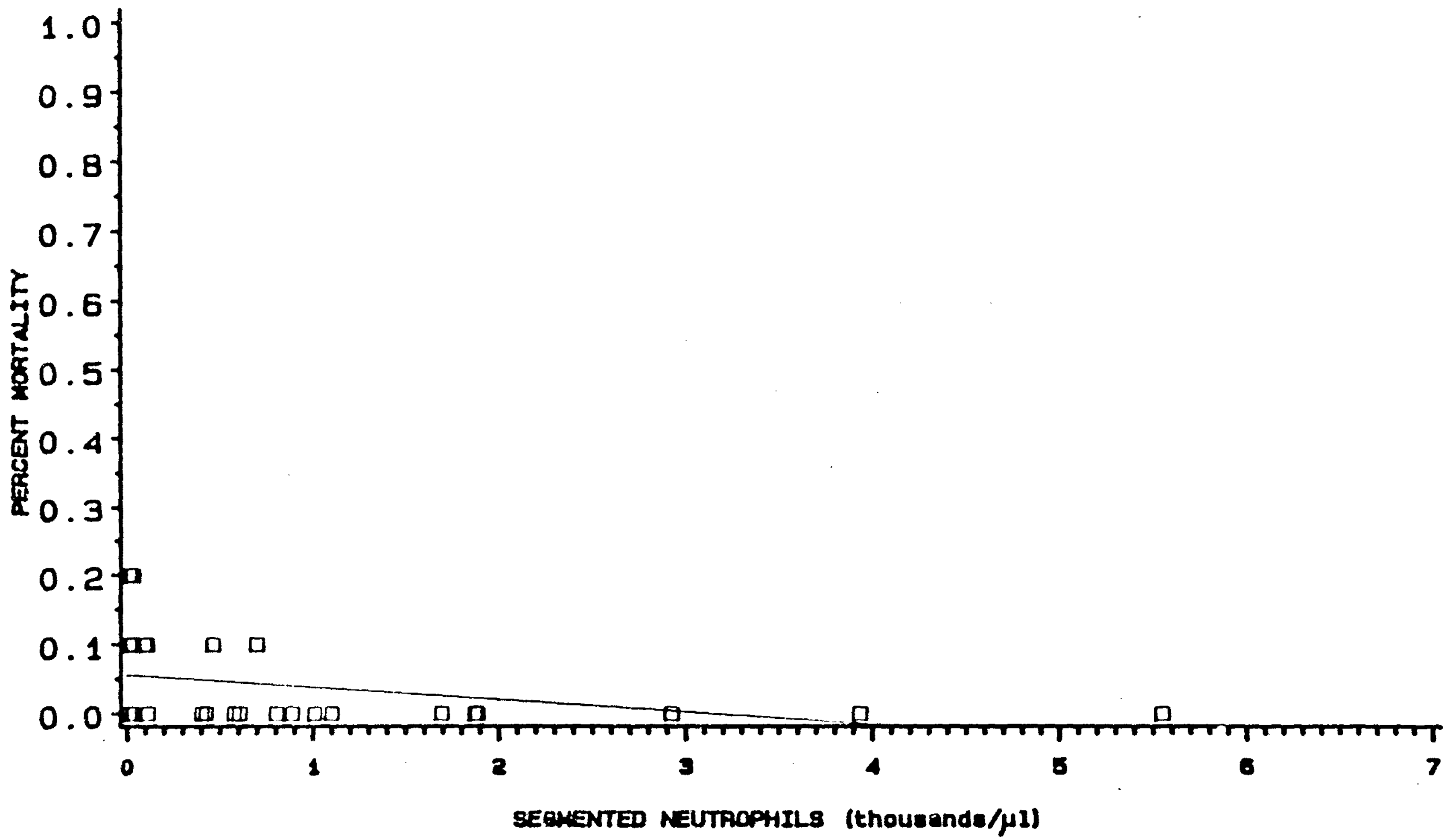


FIGURE 3.13. DAILY PERCENT MORTALITY CORRELATED WITH SEGMENTED NEUTROPHIL COUNT IN MICE DOSED WITH HD AT 26 TO 28 mg/kg RANGE

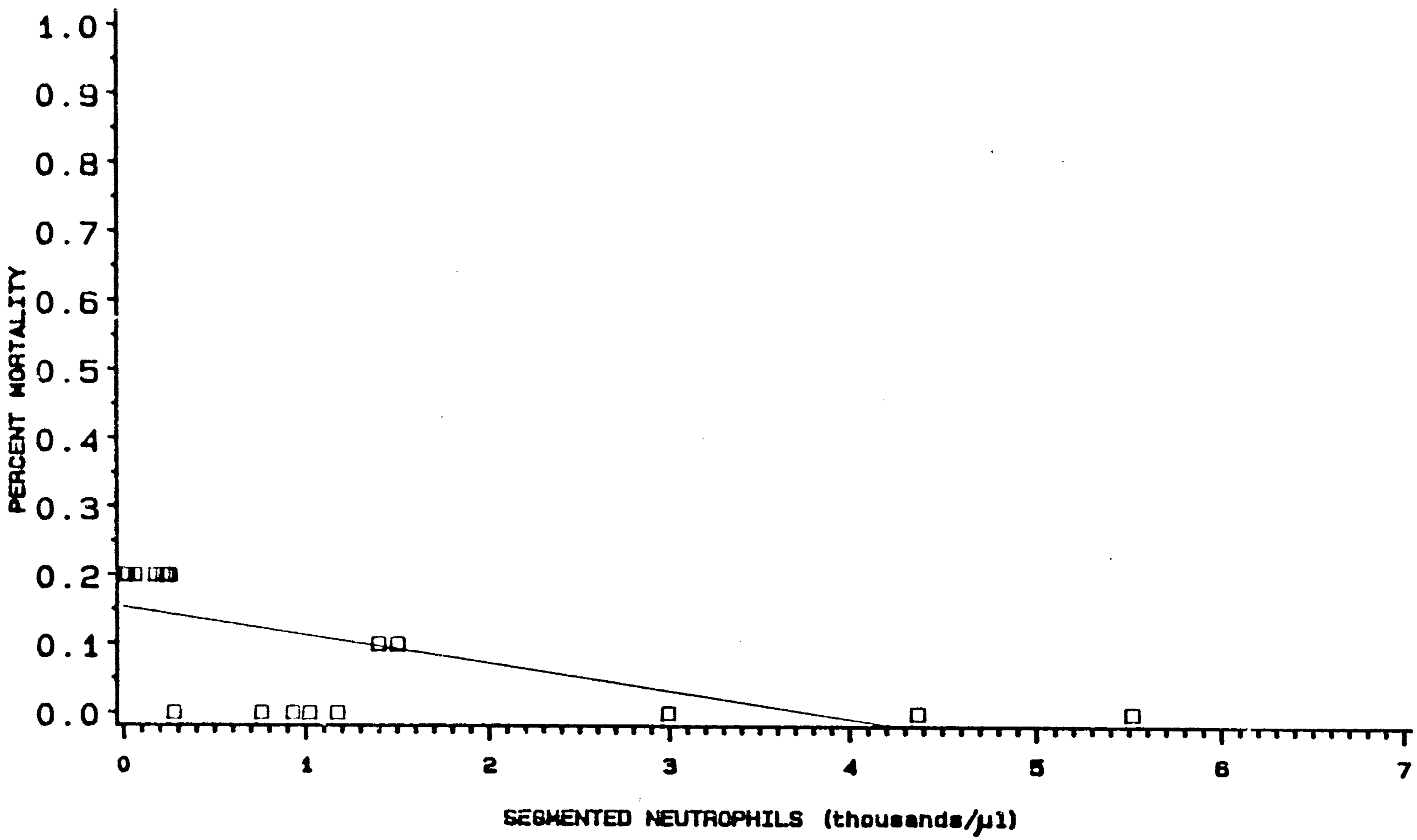


FIGURE 3.14. DAILY PERCENT MORTALITY CORRELATED WITH SEGMENTED NEUTROPHIL COUNT IN MICE DOSED WITH HD AT 29 TO 33 mg/kg RANGE

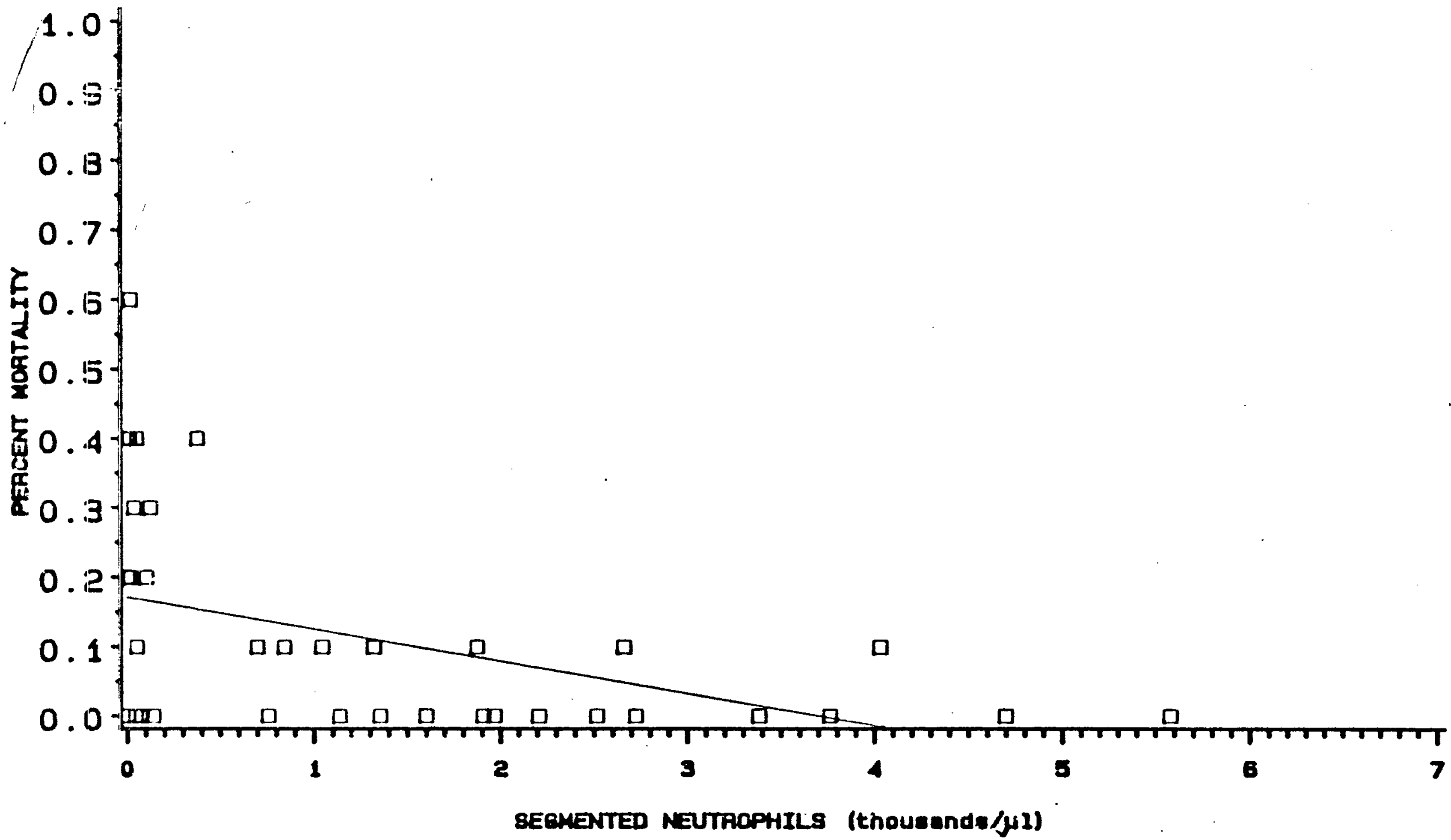


FIGURE 3.15. DAILY PERCENT MORTALITY CORRELATED WITH SEGMENTED NEUTROPHIL COUNT IN MICE DOSED WITH HD AT 34 TO 40 mg/kg RANGE

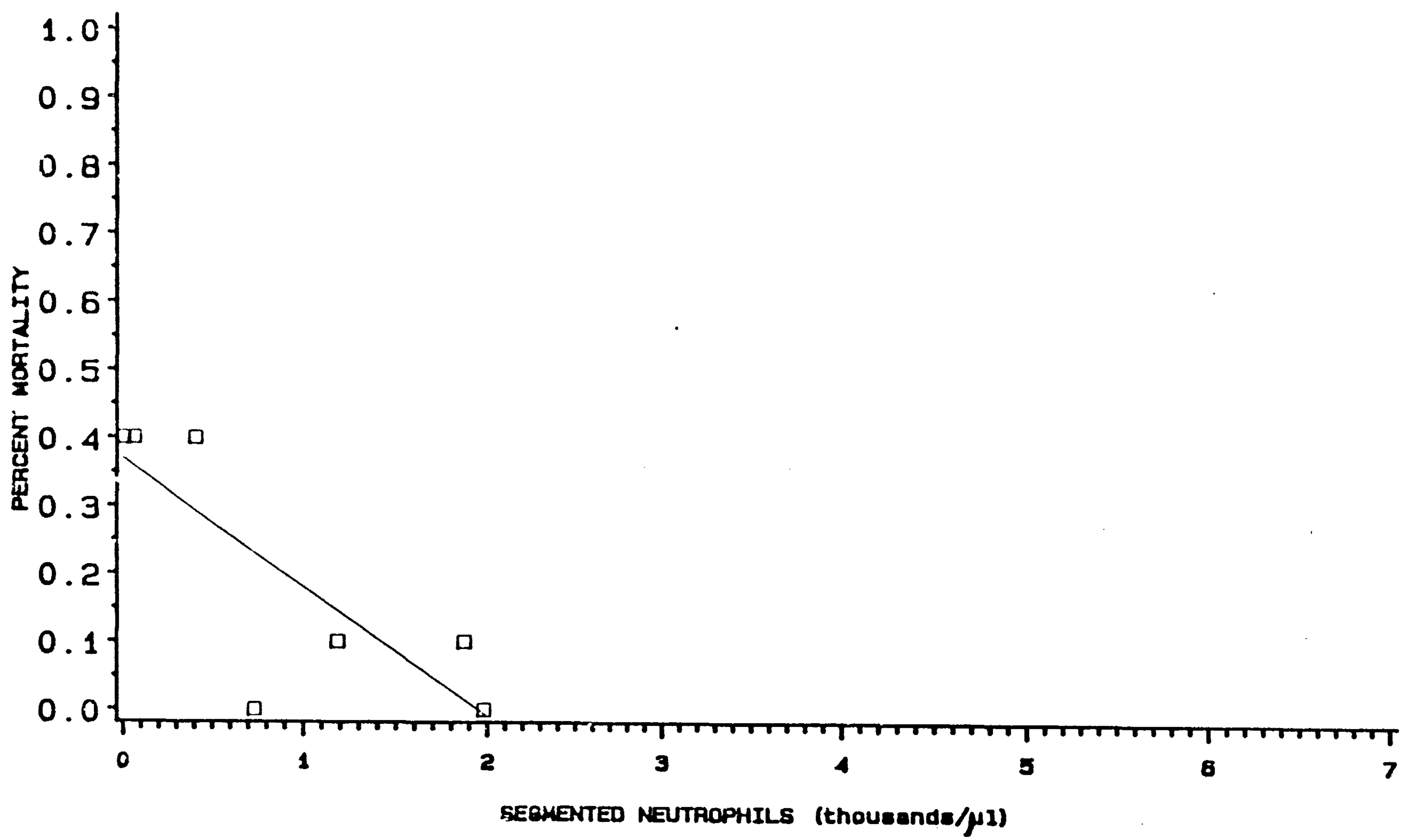


FIGURE 3.16. DAILY PERCENT MORTALITY CORRELATED WITH SEGMENTED NEUTROPHIL COUNT IN MICE DOSED WITH HD AT 4 RANGES

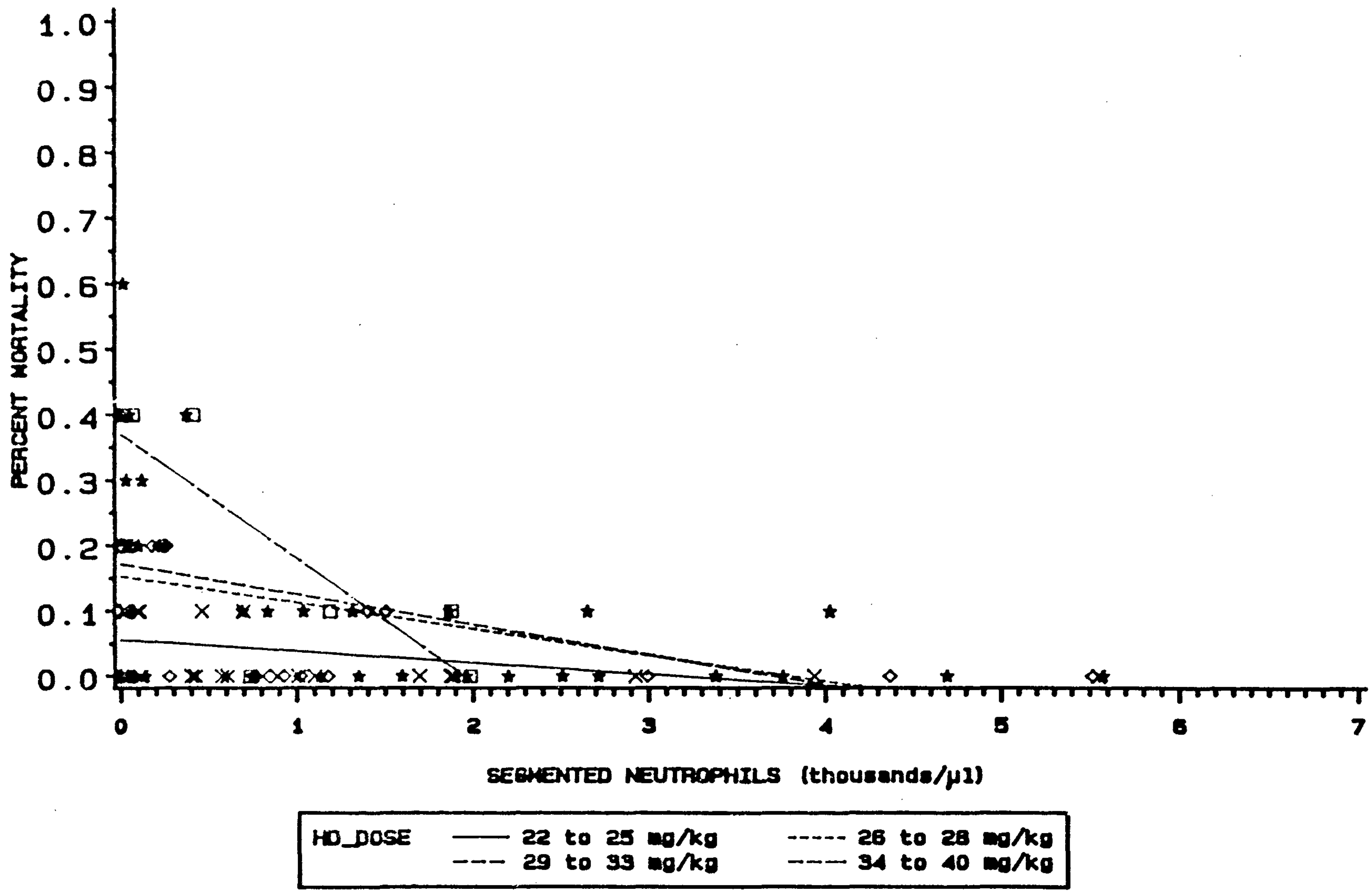


FIGURE 3.17. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{30} of HD   Inhibitor - 3-Aminobenzamide   Replicate - 1

FREQUENCY BLOCK CHART

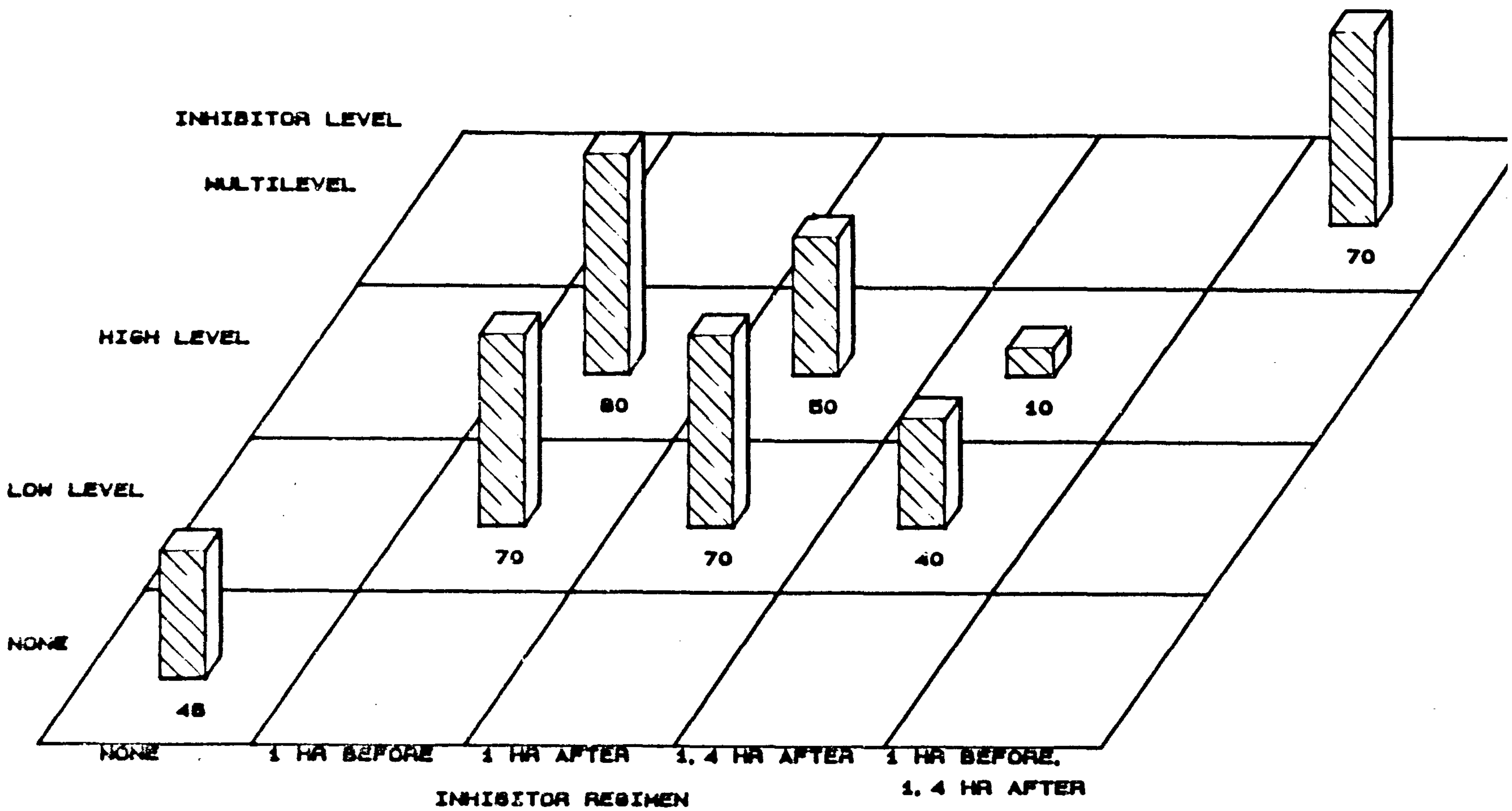


FIGURE 3.18. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose LD_{30} of HD   Inhibitor - 3-Aminobenzamide   Replicate - 2

FREQUENCY BLOCK CHART

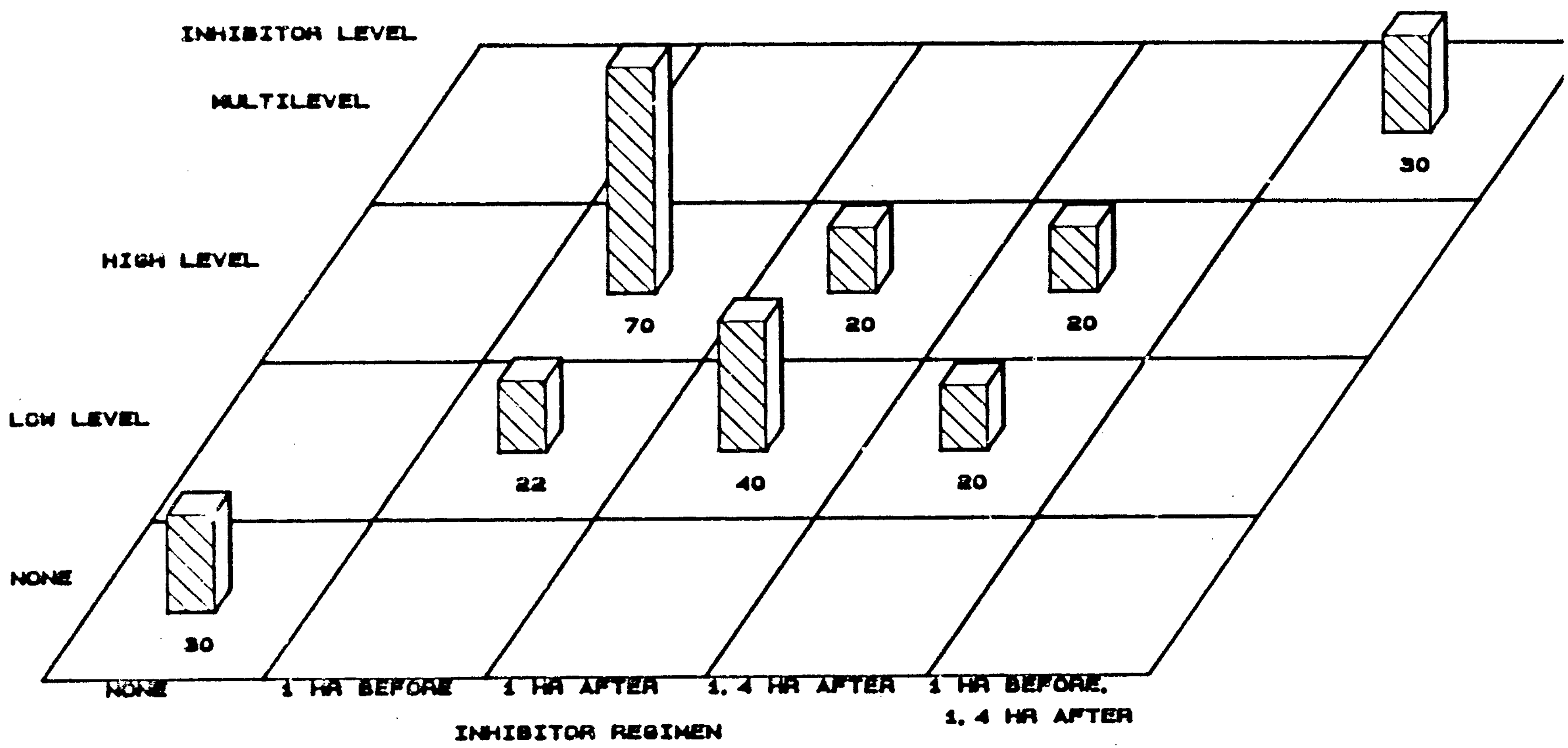


FIGURE 3.19. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{30} of HD   Inhibitor - Nicotinic Acid   Replicate - 1

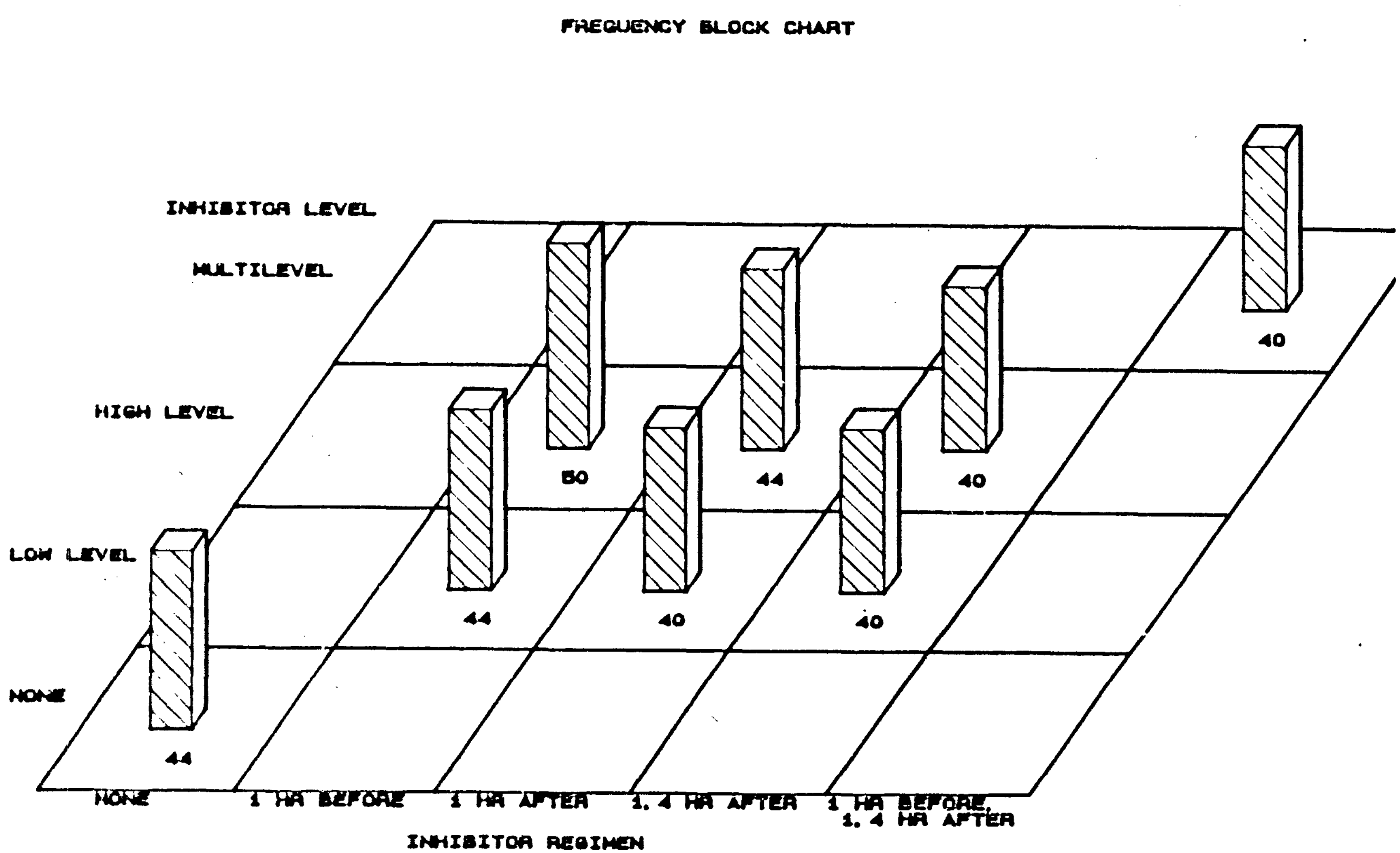


FIGURE 3.20. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{30} of HD   Inhibitor - Nicotinic Acid   Replicate - 2

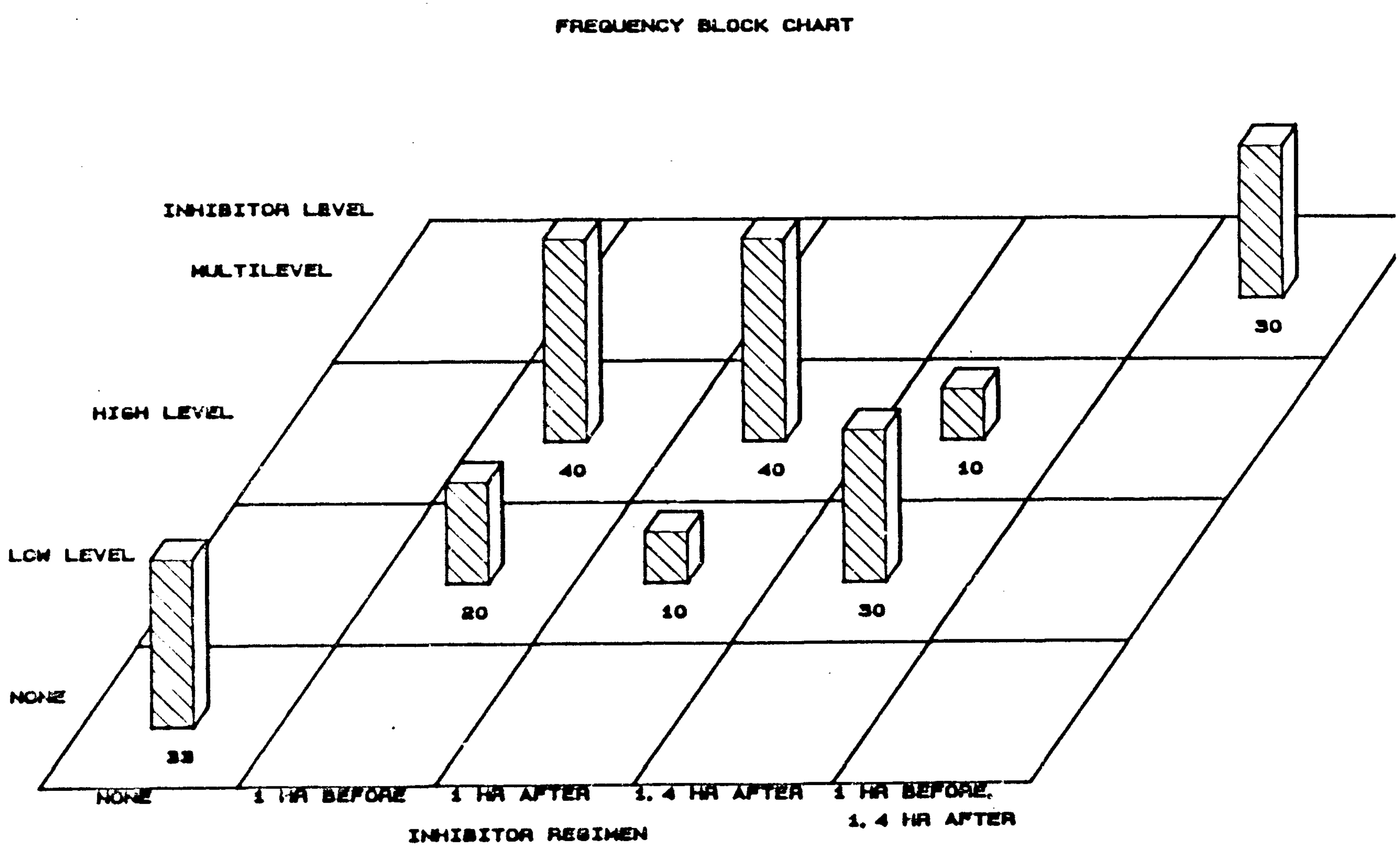


FIGURE 3.21. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{30} of HD   Inhibitor - Nicotinamide   Replicate - 1

FREQUENCY BLOCK CHART

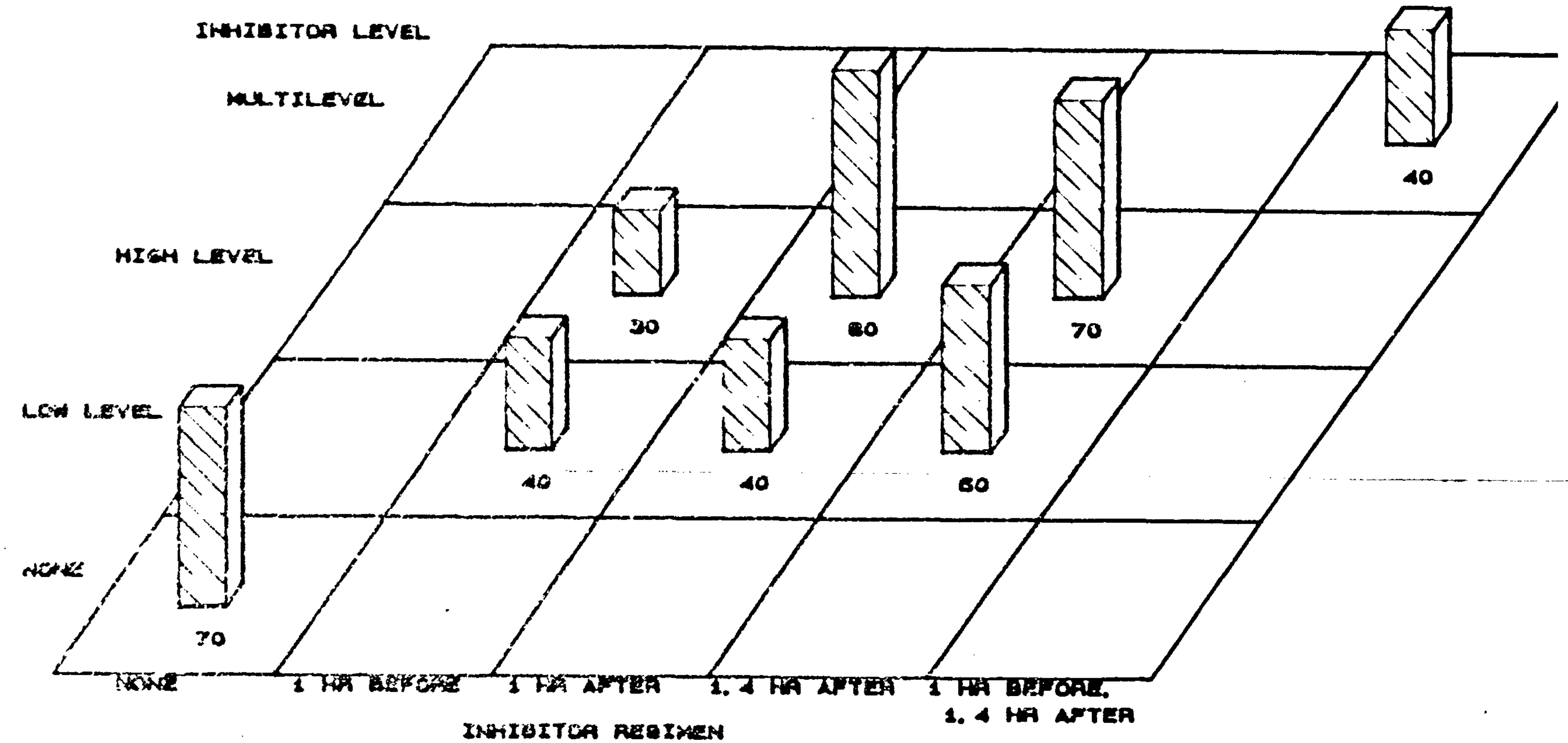


FIGURE 3.22. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{30} of HD   Inhibitor - Nicotinamide   Replicate - 2

FREQUENCY BLOCK CHART

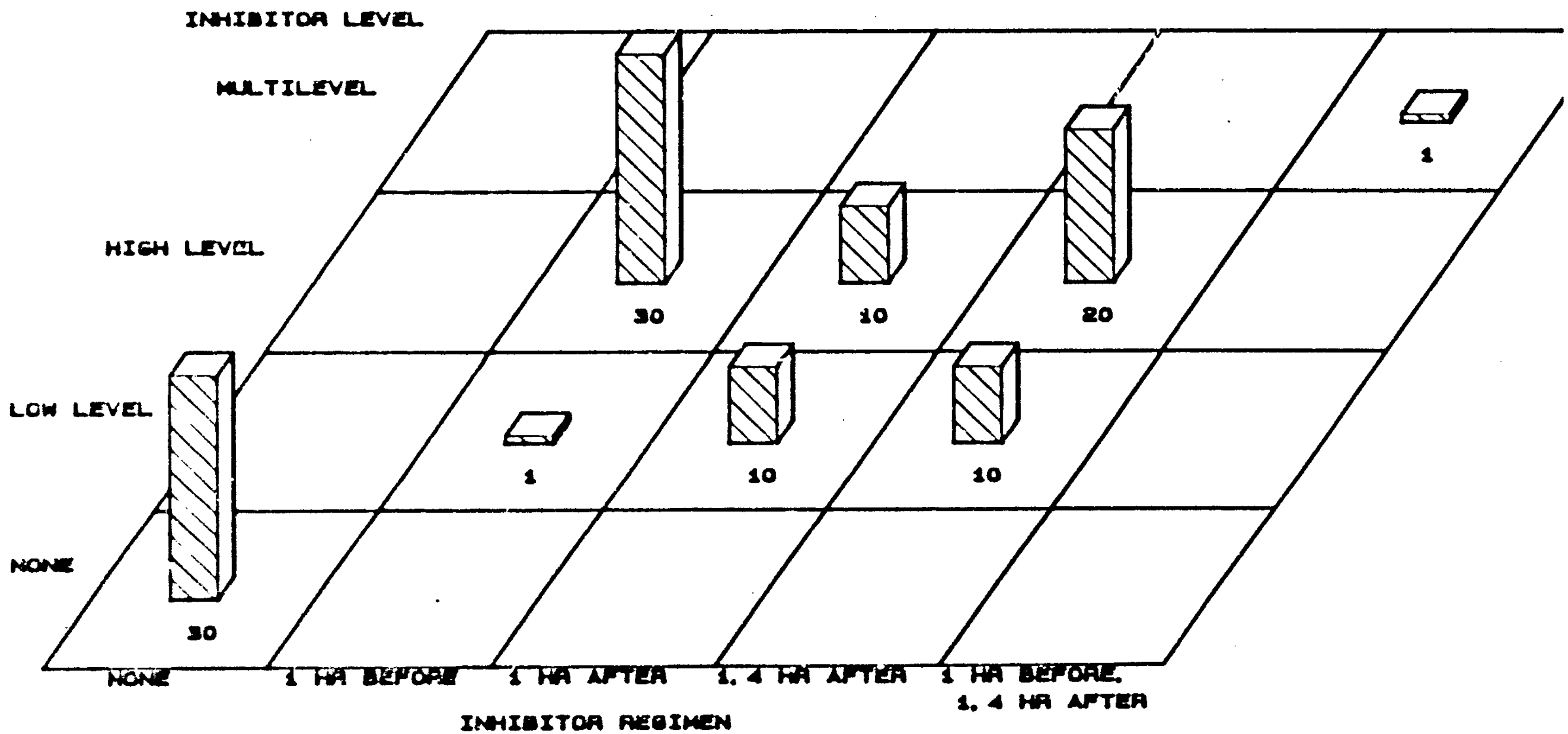


FIGURE 3.23. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{50} of HD   Inhibitor - 3-Aminobenzamide   Replicate - 1

FREQUENCY BLOCK CHART

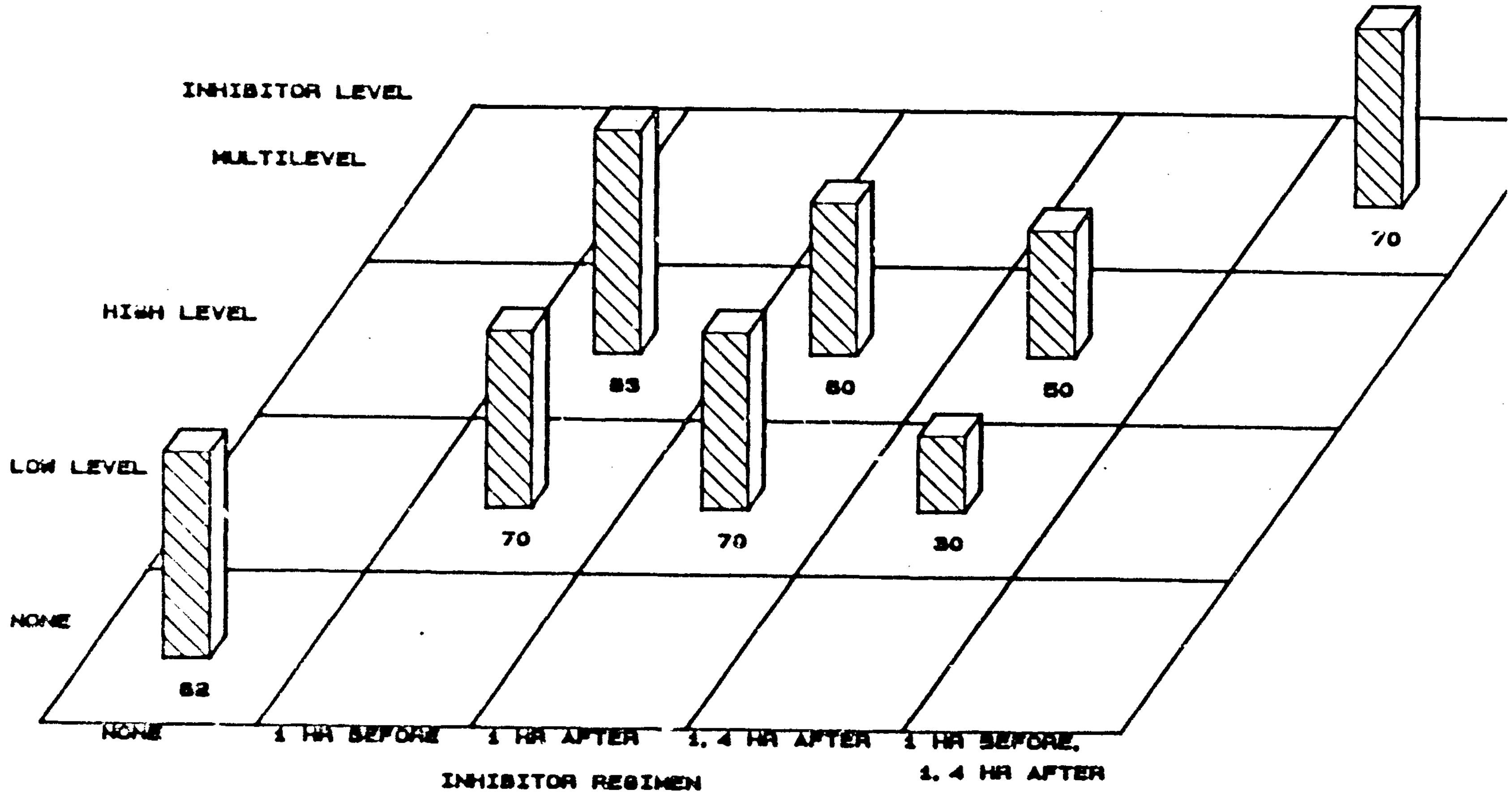


FIGURE 3.24. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{60} of HD   Inhibitor - 3-Aminobenzamide   Replicate - 2

FREQUENCY BLOCK CHART

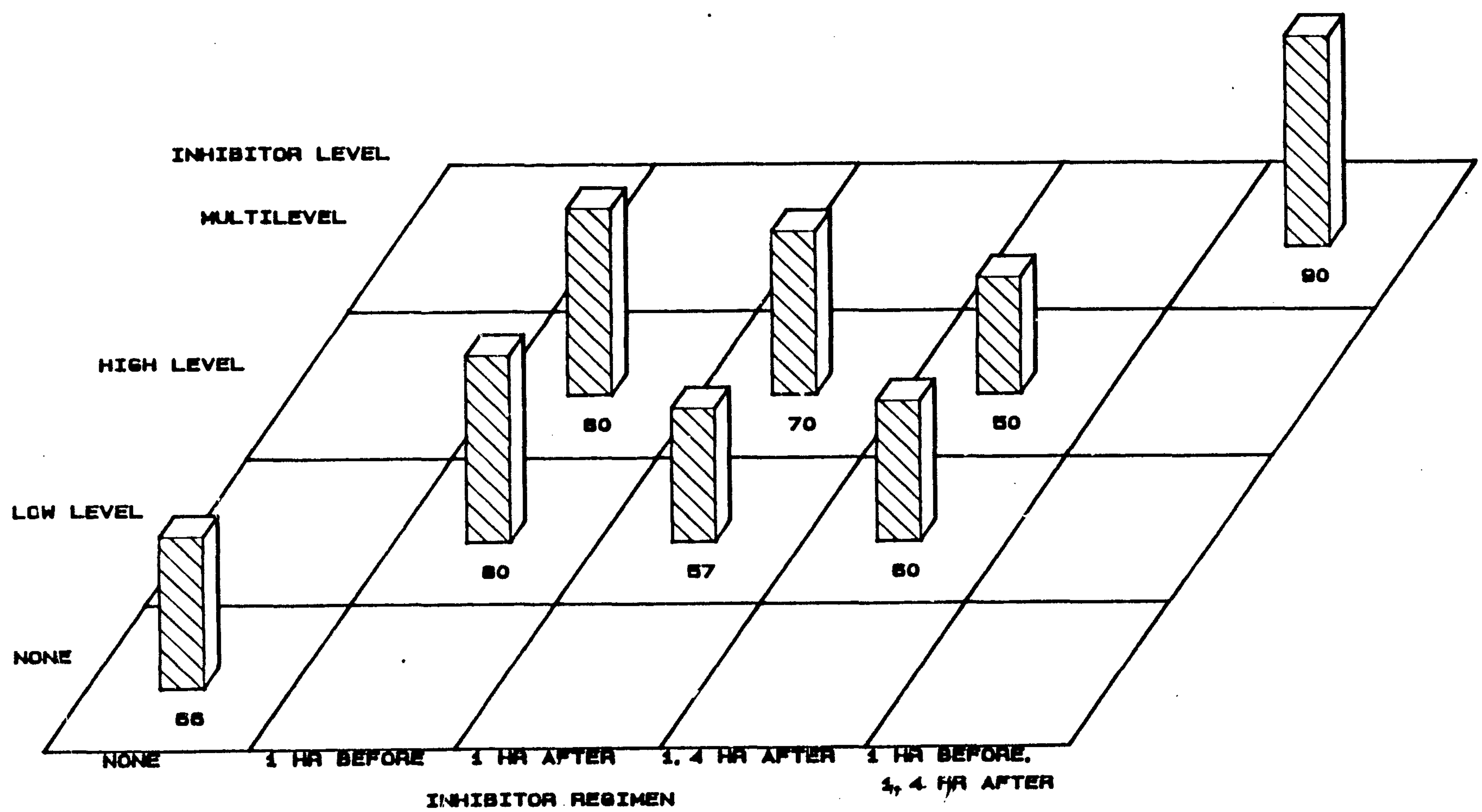


FIGURE 3.25. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{60} of HD Inhibitor - Nicotinamide Replicate - 1

FREQUENCY BLOCK CHART

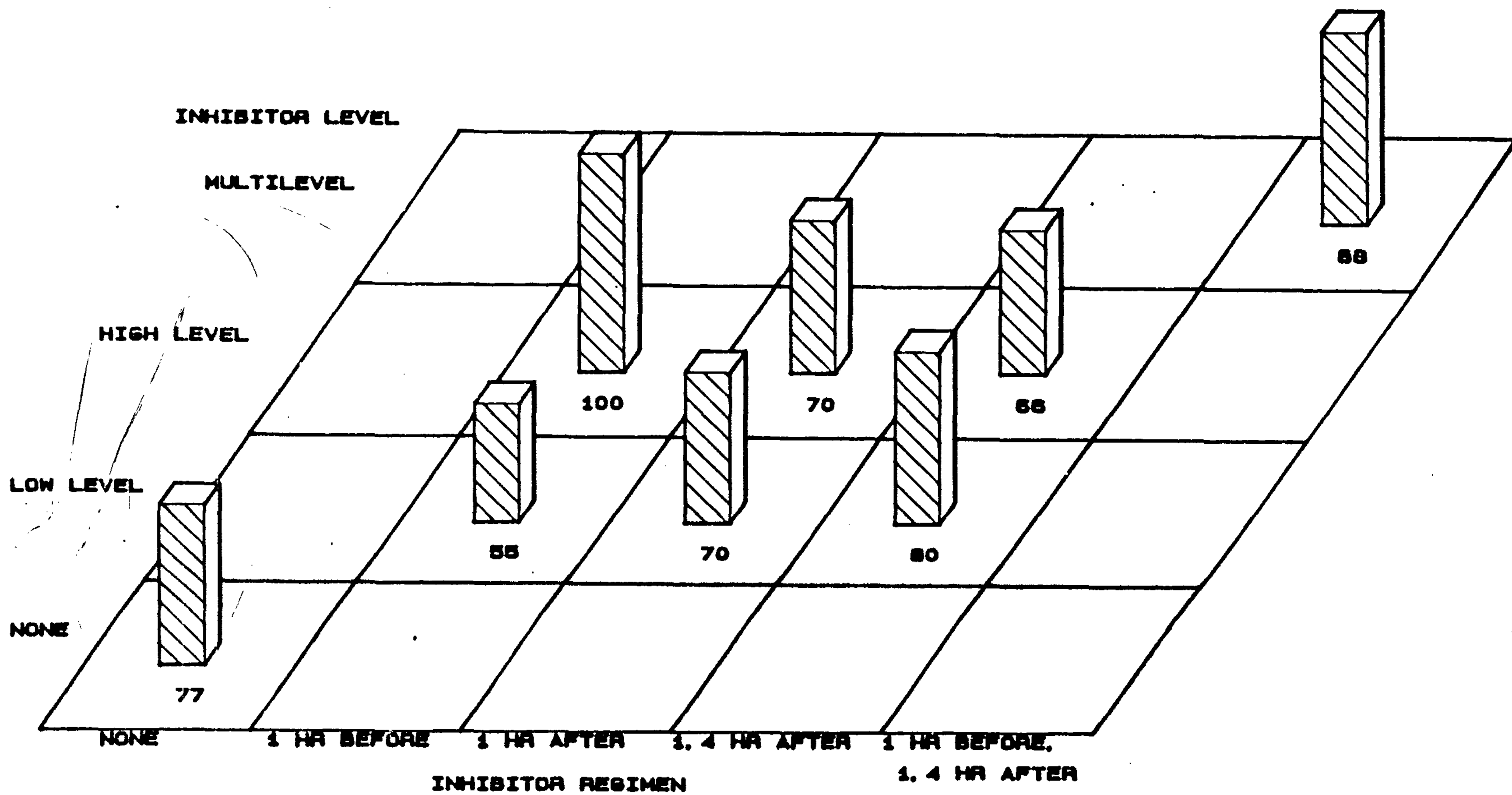


FIGURE 3.26. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{60} of HD   Inhibitor - Nicotinamide   Replicate - 2

FREQUENCY BLOCK CHART

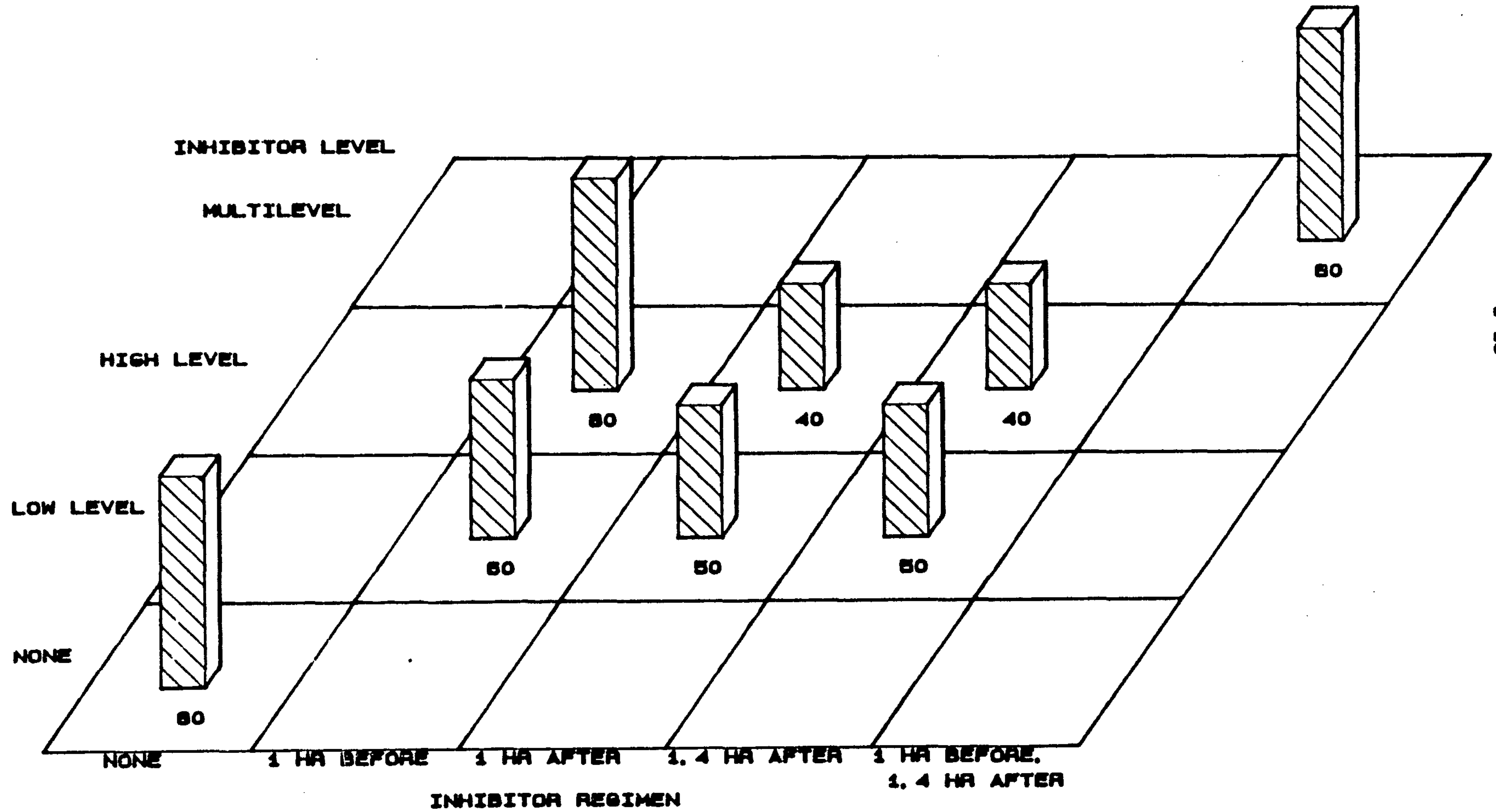


FIGURE 3.27. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{60} of HD Inhibitor - Nicotinic Acid Replicate - 1

FREQUENCY BLOCK CHART

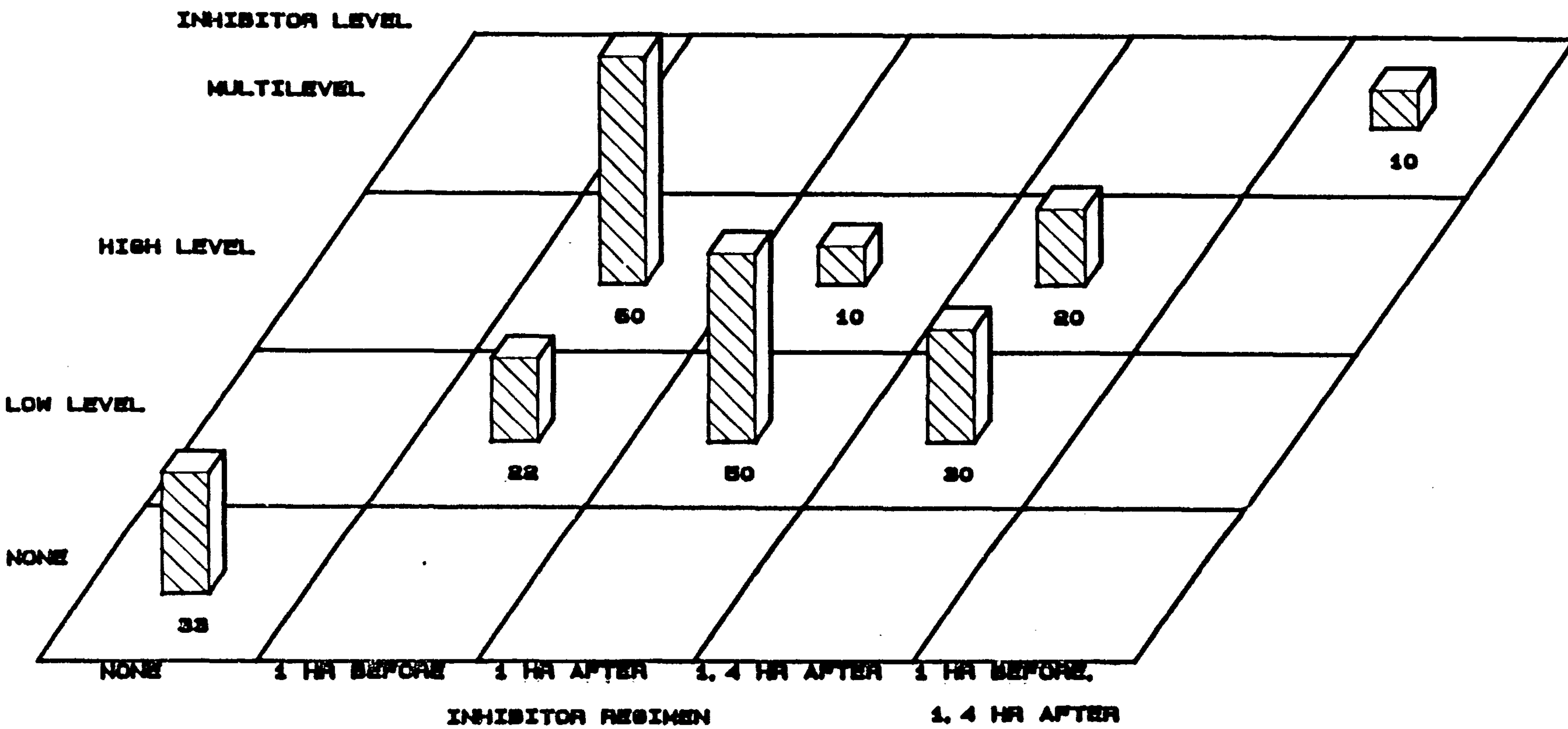


FIGURE 3.28. PERCENT MORTALITY AMONG HD-DOSED GROUPS

Target Dose - LD_{60} of HD   Inhibitor - Nicotinic Acid   Replicate - 2

FREQUENCY BLOCK CHART

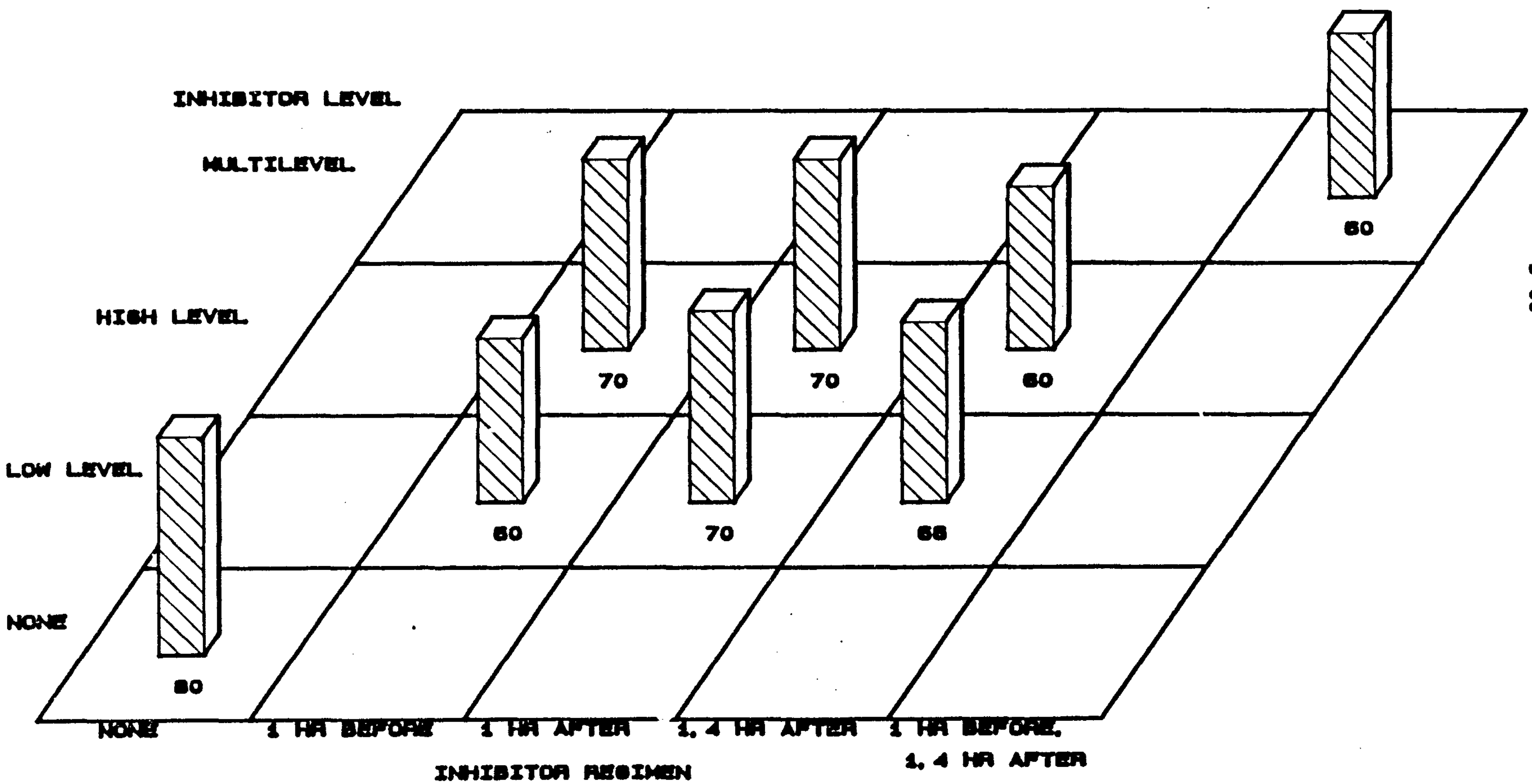
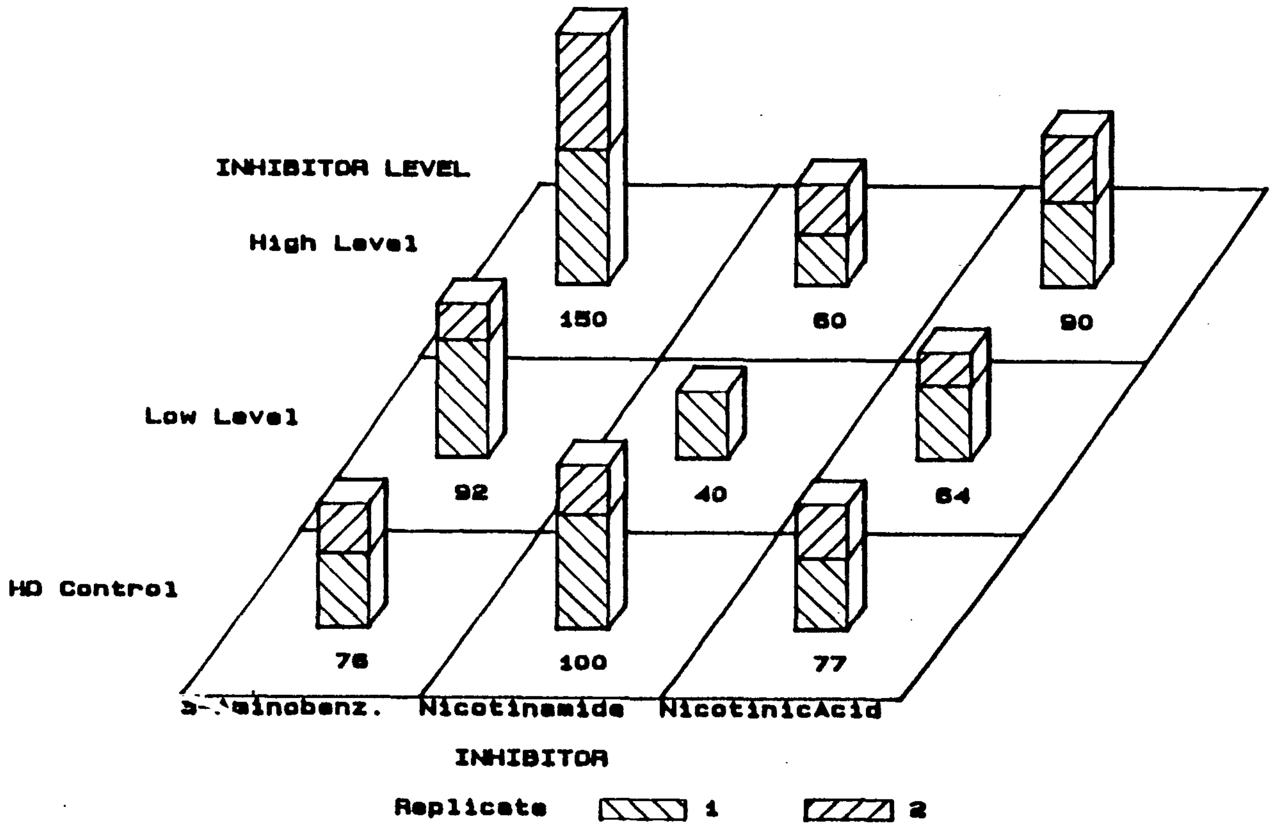


FIGURE 3.29. PERCENT MORTALITY AMONG GROUPS RECEIVING INHIBITOR AT 1 HR BEFORE THE HD DOSE

Target Dose - LD_{30} of HD

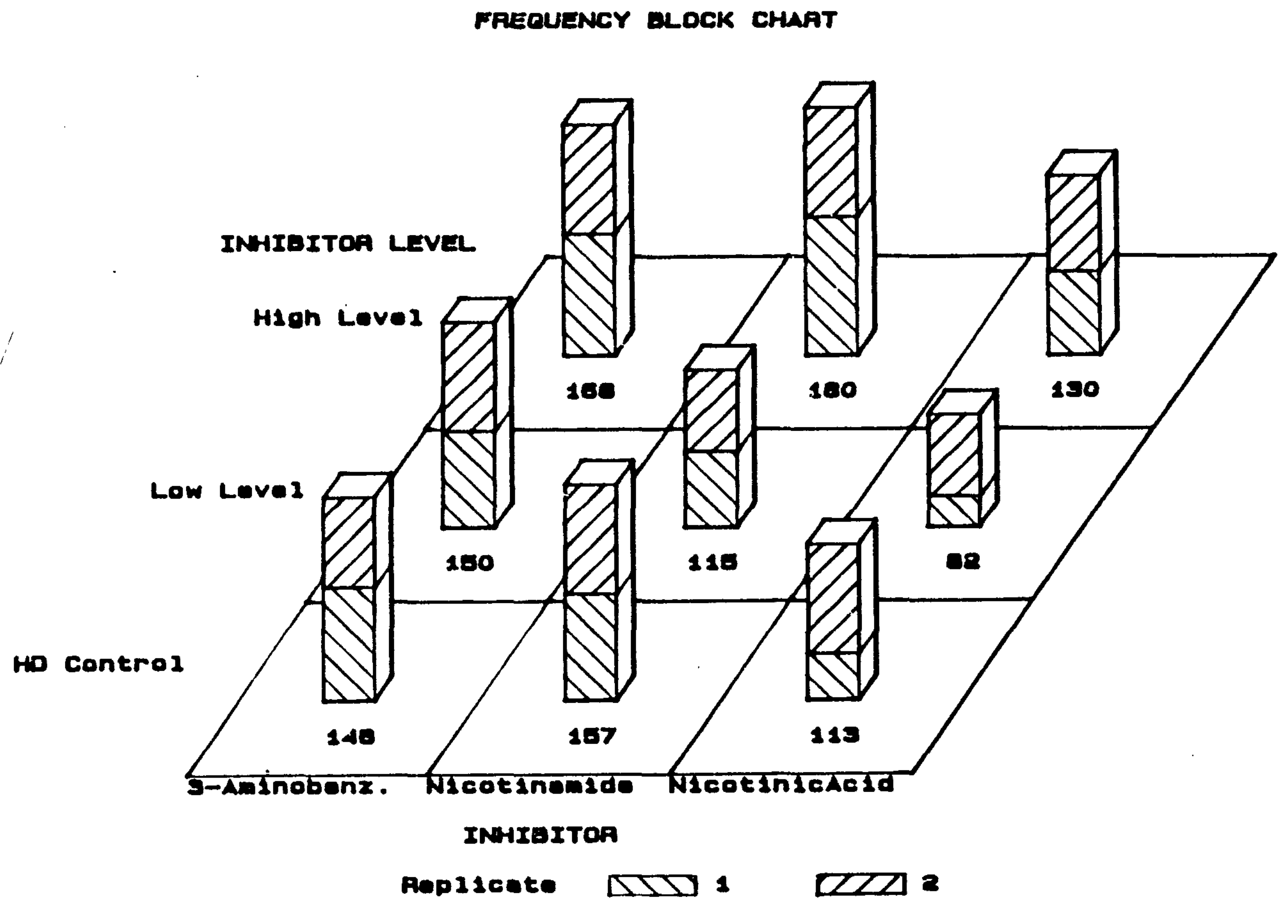
FREQUENCY BLOCK CHART



Numbers at the bases of the blocks are percent mortality added across replicates

FIGURE 3.30. PERCENT MORTALITY AMONG GROUPS RECEIVING INHIBITOR AT 1 HR BEFORE THE HD DOSE

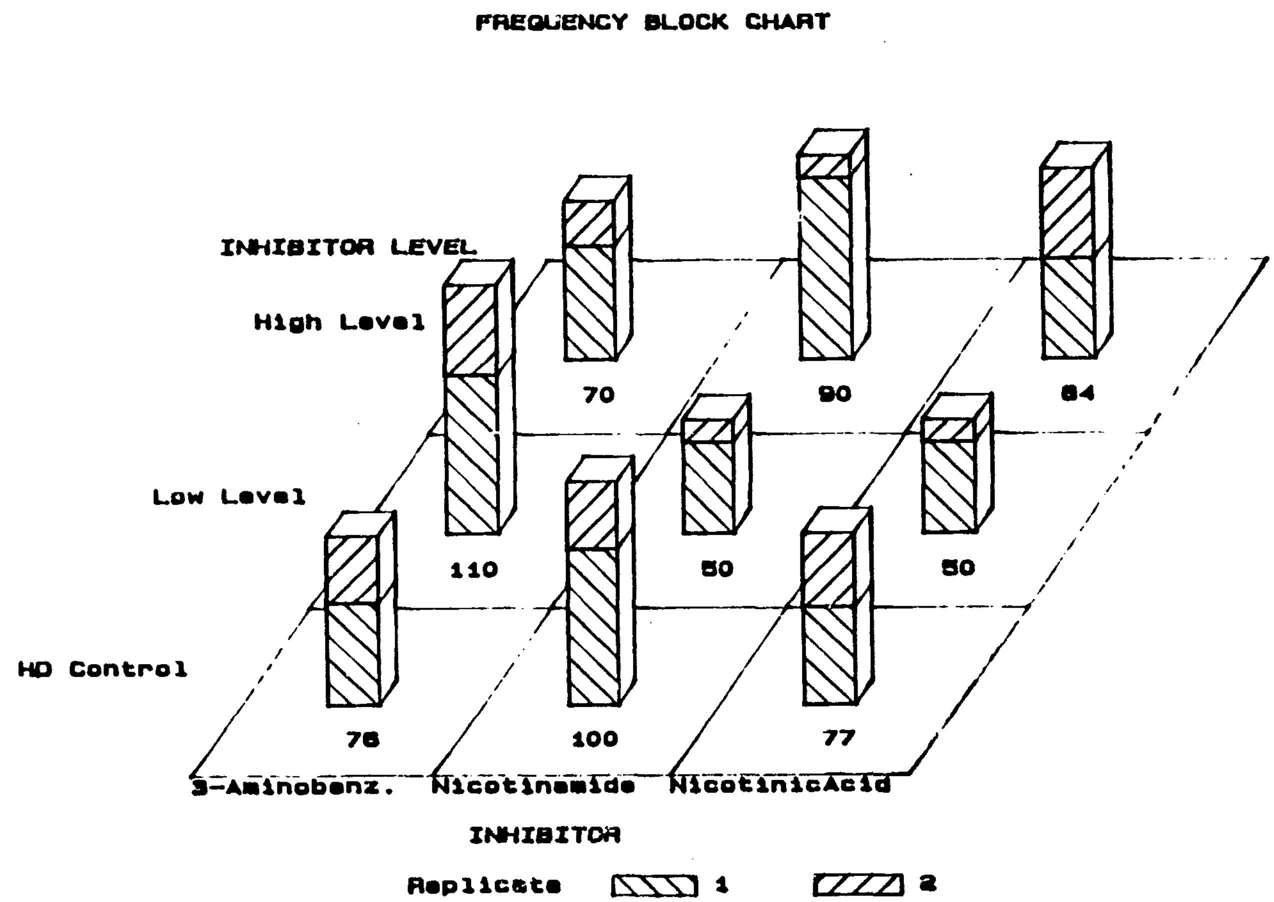
Target Dose - LD_{60} of HD



Numbers at the bases of the blocks are percent mortality added across replicates

FIGURE 3.31. PERCENT MORTALITY AMONG GROUPS RECEIVING INHIBITOR AT 1 HR AFTER THE HD DOSE

Target Dose - LD_{30} of HD

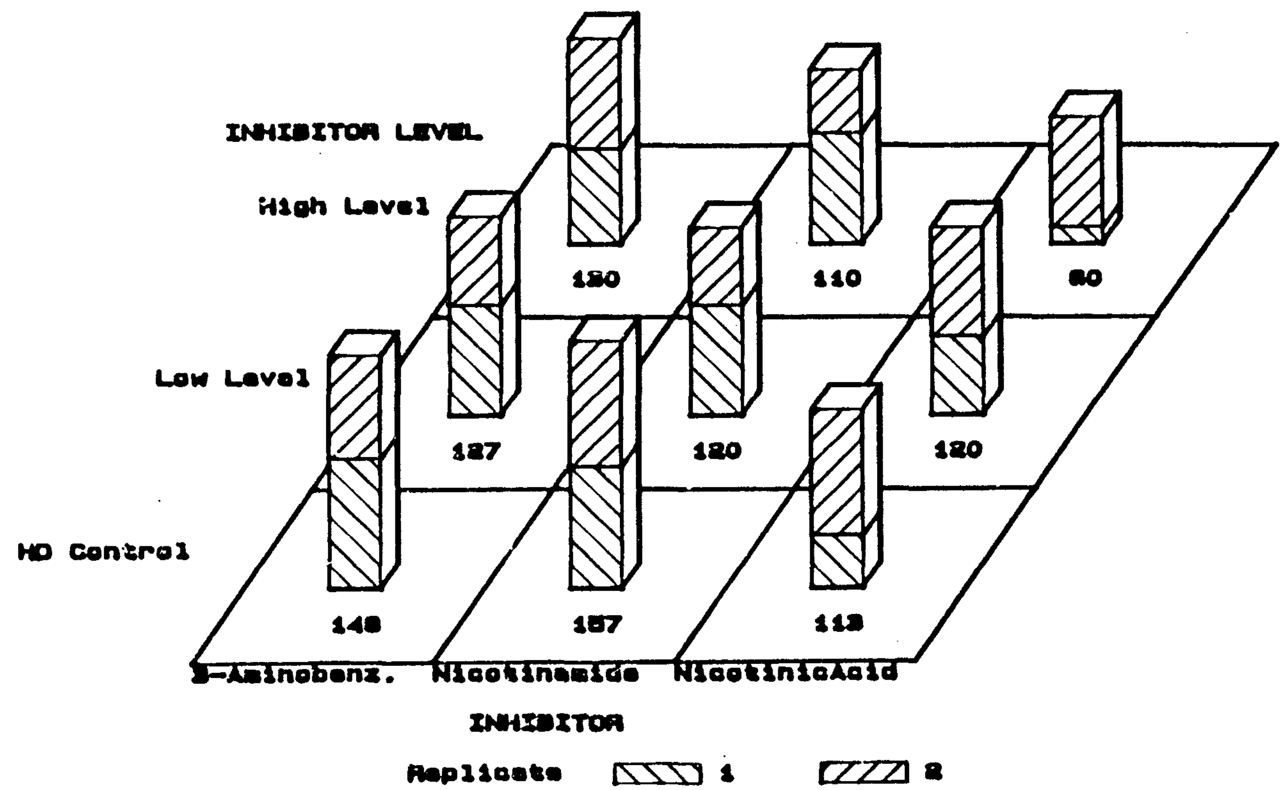


Numbers at the bases of the blocks are percent mortality added across replicates

FIGURE 3.32. PERCENT MORTALITY AMONG GROUPS RECEIVING INHIBITOR AT 1 HR AFTER THE HD DOSE

Target Dose - LD_{60} of HD

FREQUENCY BLOCK CHART

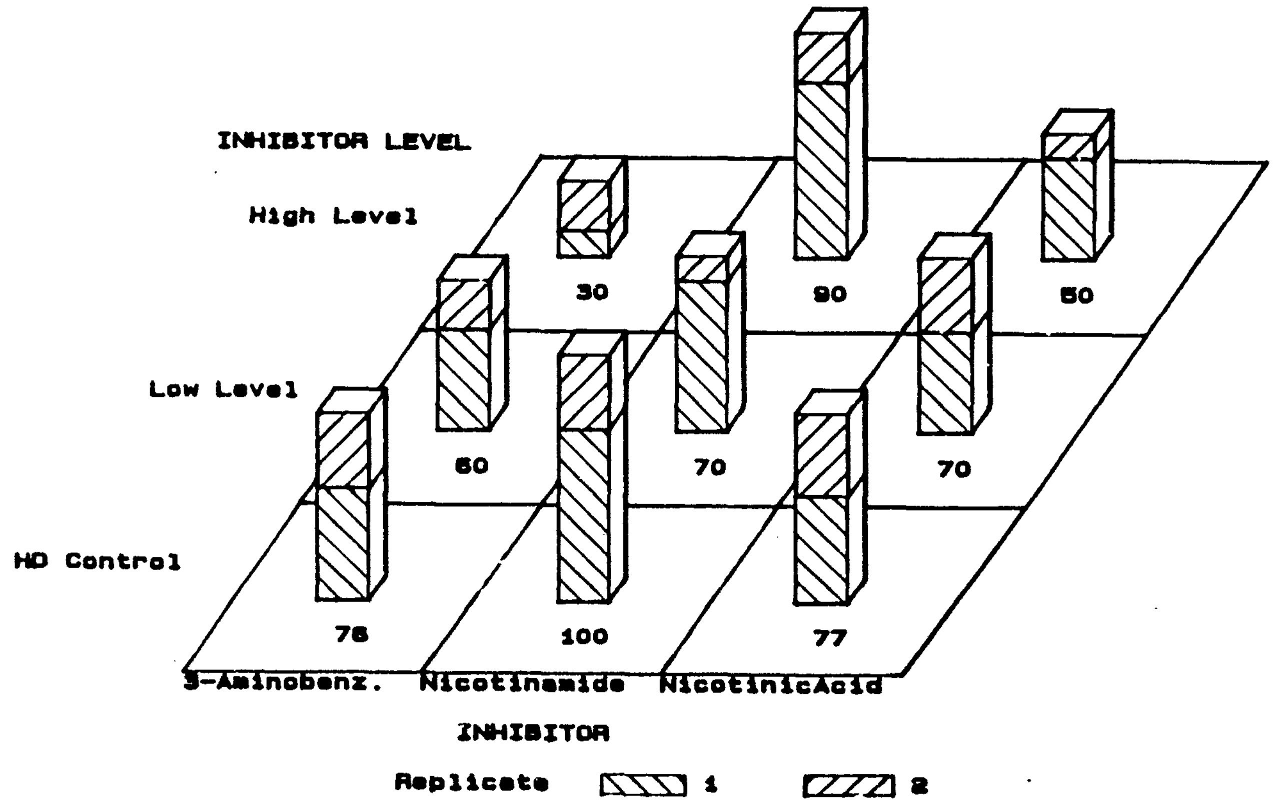


Numbers at the bases of the blocks are percent mortality added across replicates

FIGURE 3.33. PERCENT MORTALITY AMONG GROUPS RECEIVING INHIBITOR AT 1 AND 4 HR AFTER THE HD DOSE

Target Dose - LD_{30} of HD

FREQUENCY BLOCK CHART

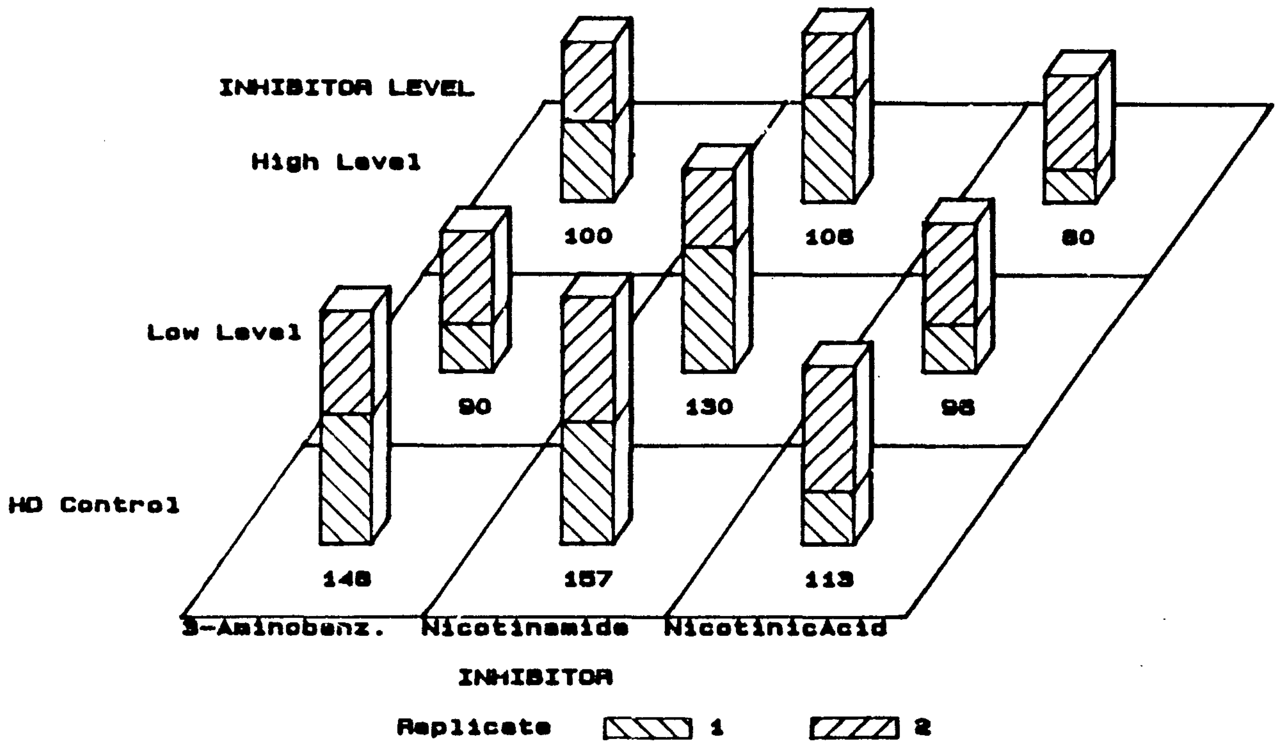


Numbers at the bases of the blocks are percent mortality added across replicates

FIGURE 3.34. PERCENT MORTALITY AMONG GROUPS RECEIVING INHIBITOR AT 1 AND 4 HR AFTER THE HD DOSE

Target Dose - LD_{60} of HD

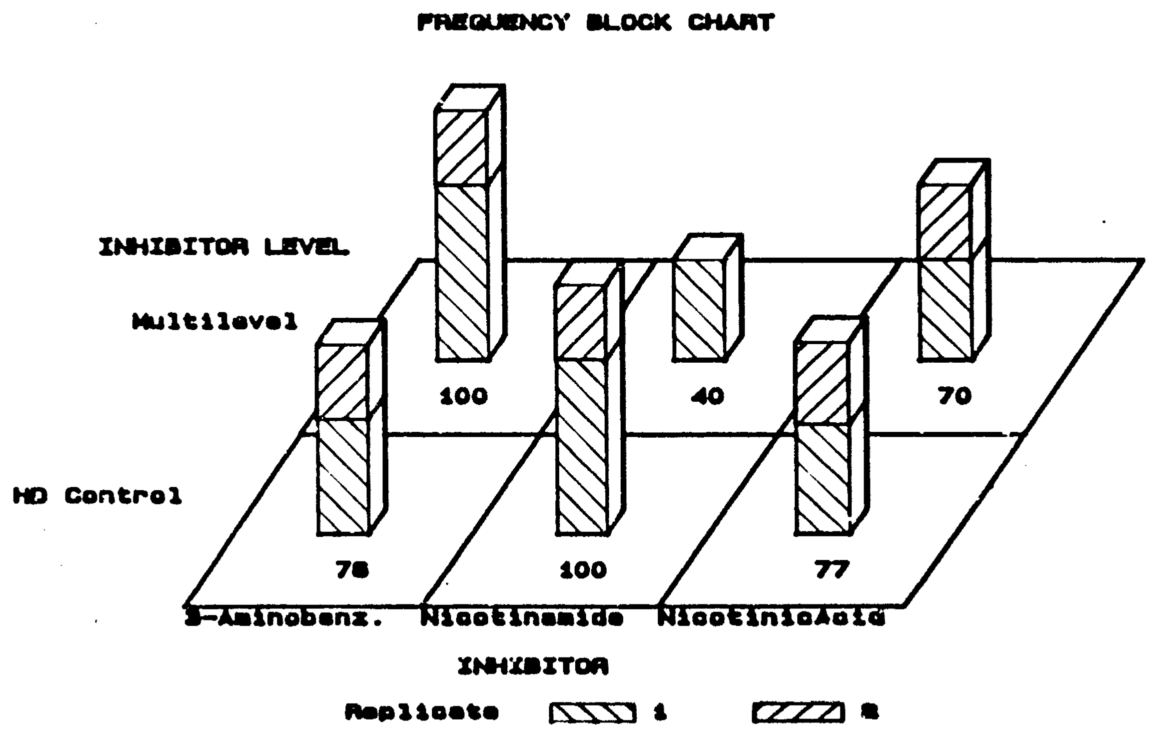
FREQUENCY BLOCK CHART



Numbers at the bases of the blocks are percent mortality added across replicates

FIGURE 3.35. PERCENT MORTALITY AMONG GROUPS RECEIVING INHIBITOR AT 1 HR BEFORE AND 1 AND 4 HR AFTER THE HD DOSE

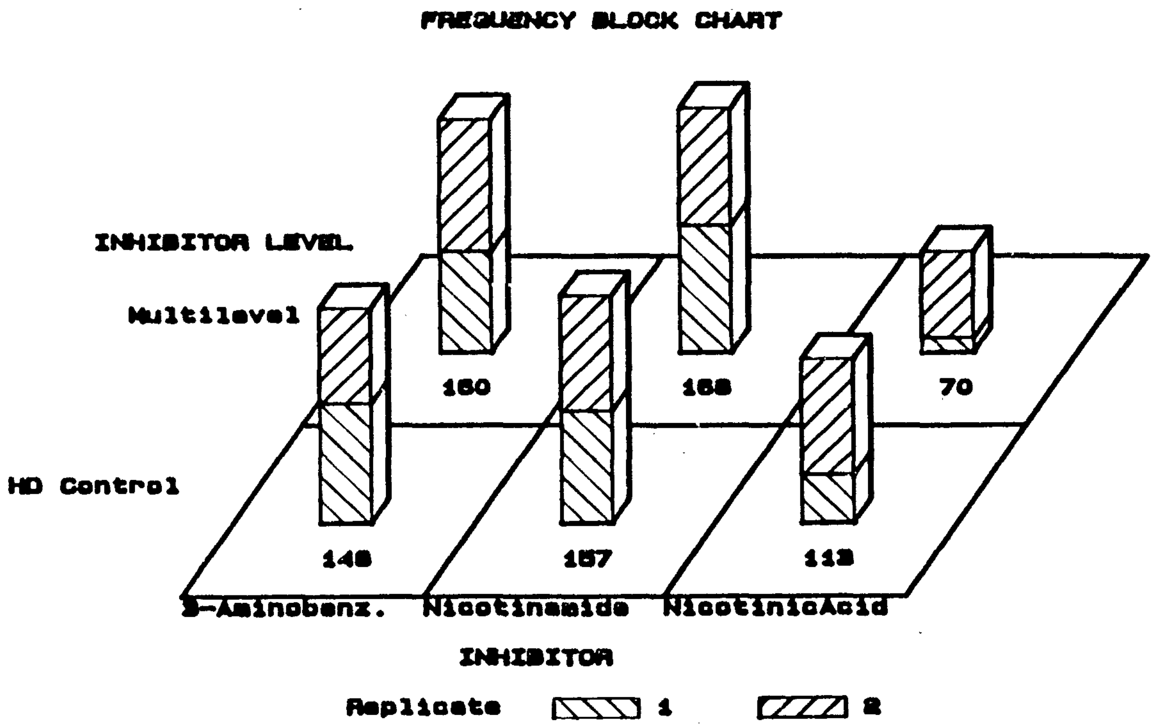
Target Dose - LD_{30} of HD



Numbers at the bases of the blocks are percent mortality added across replicates

FIGURE 3.36. PERCENT MORTALITY AMONG GROUPS RECEIVING INHIBITOR AT 1 HR BEFORE AND 1 AND 4 HR AFTER THE HD DOSE

Target Dose - LD_{60} of HD



Numbers at the bases of the blocks are percent mortality added across replicates

FIGURE 3.37. COMPARISON OF MORTALITY AMONG HD-DOSED GROUPS ACROSS REPLICATES

Target HD Dose - LD_{30} of HD Inhibitor - 3-Aminobenzamide

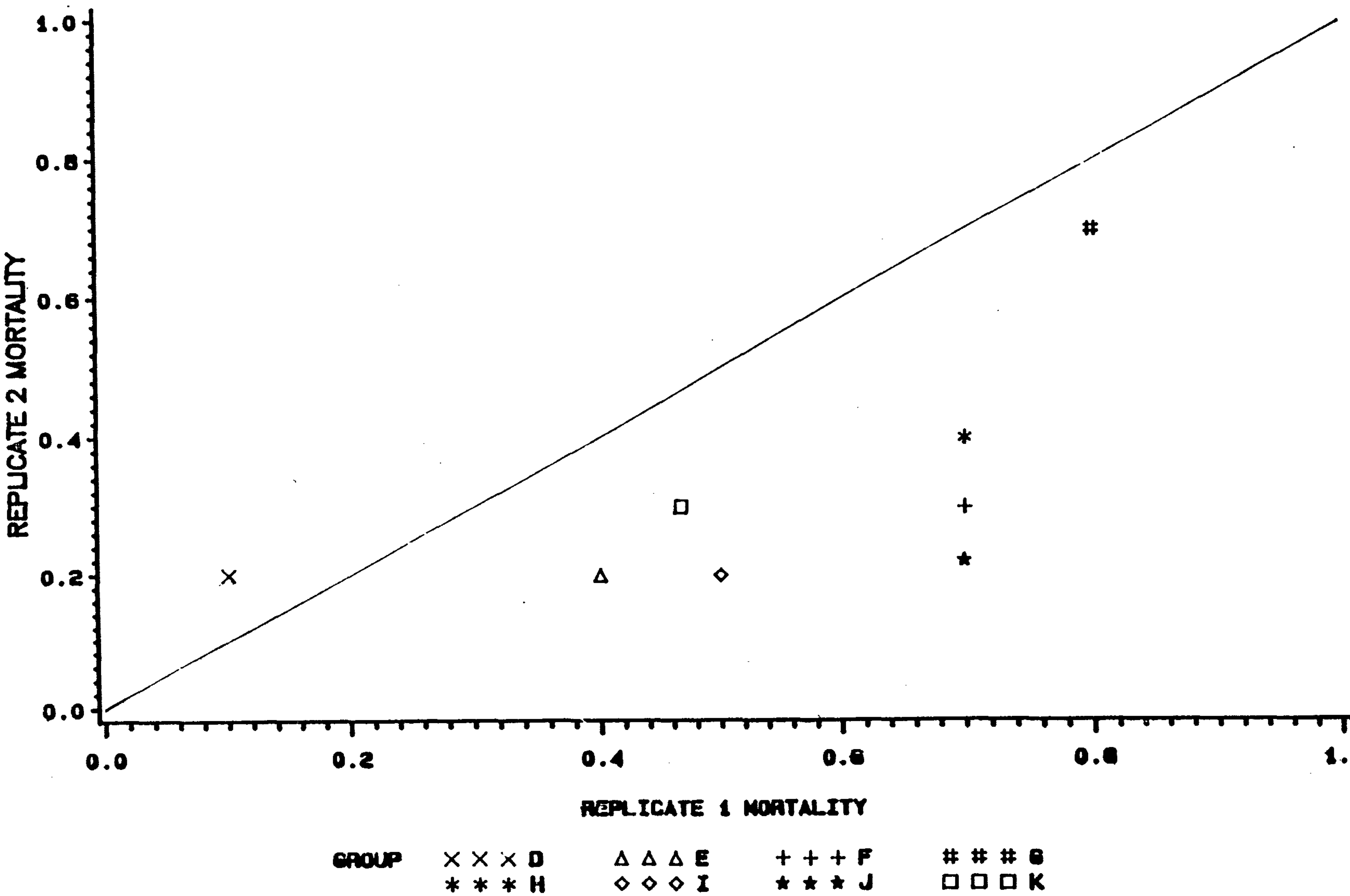


FIGURE 3.38. COMPARISON OF MORTALITY AMONG HD-DOSED GROUPS ACROSS REPLICATES

Target HD Dose - LD_{30} of HD   Inhibitor - Nicotinic Acid

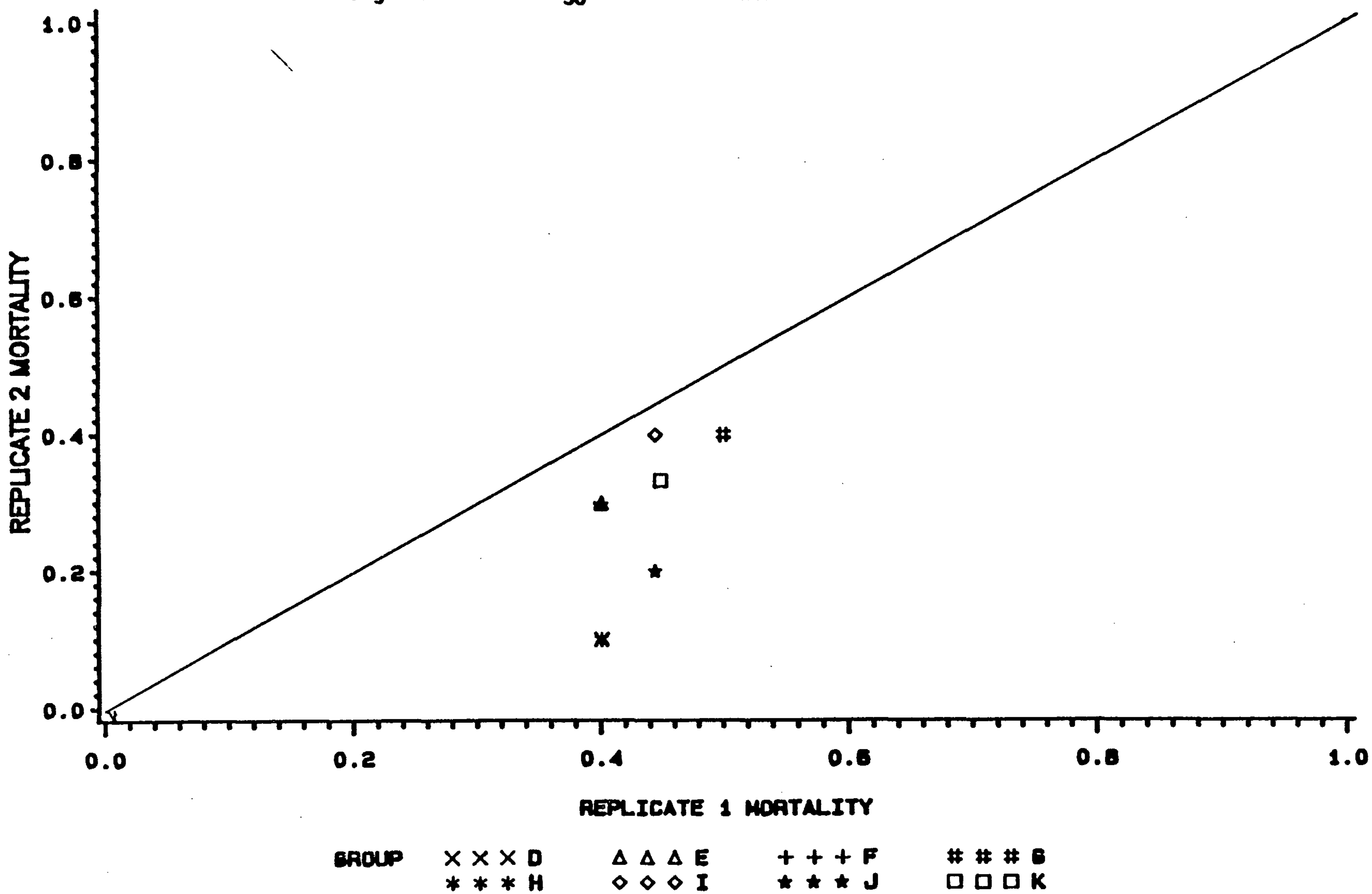


FIGURE 3.39. COMPARISON OF MORTALITY AMONG HD-DOSED GROUPS ACROSS REPLICATES

Target HD Dose - LD_{30} of HD   Inhibitor - Nicotinamide

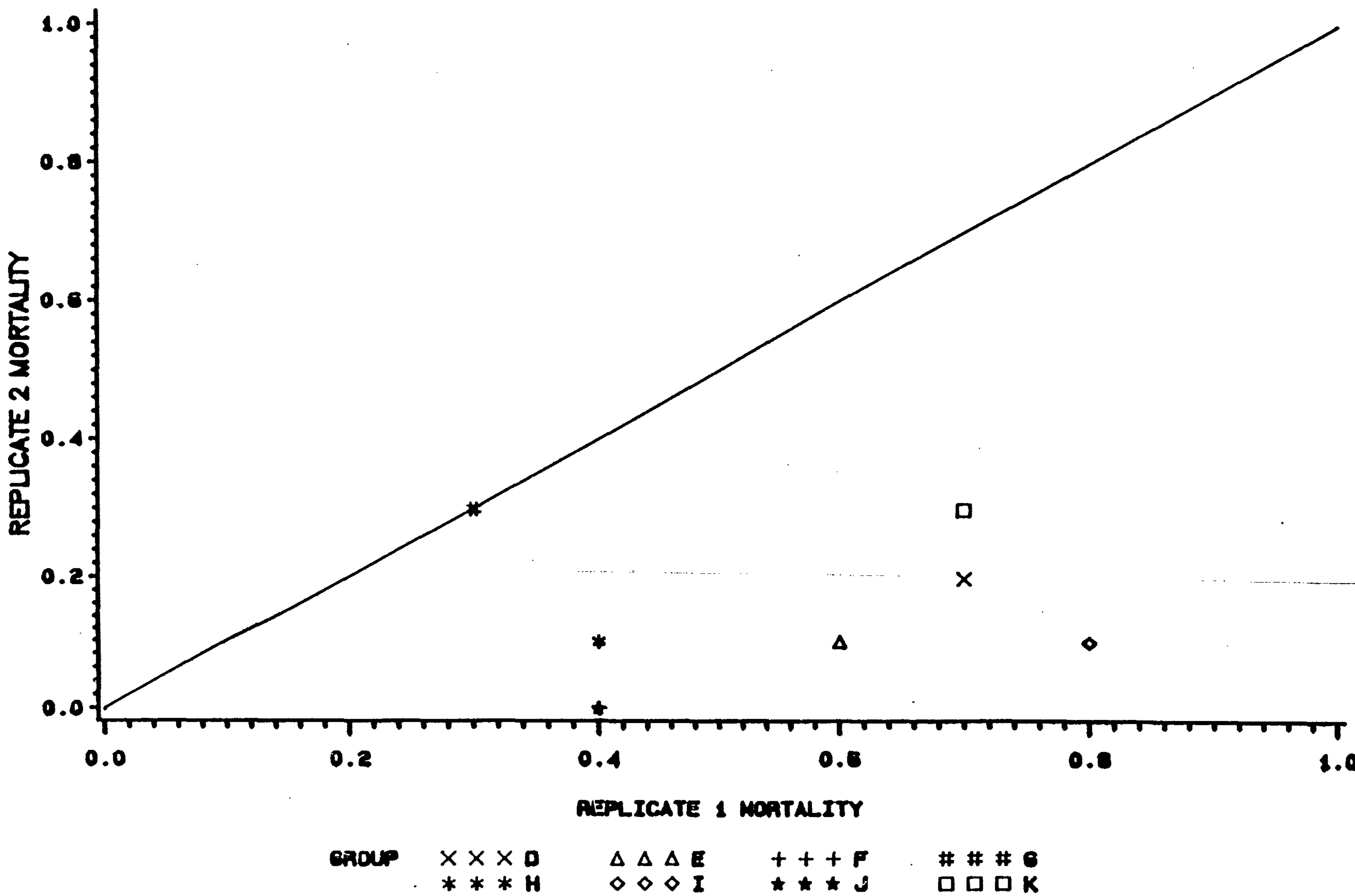


FIGURE 3.40. COMPARISON OF MORTALITY AMONG HD-DOSED GROUPS ACROSS REPLICATES

Target HD Dose - LD_{60} of HD   Inhibitor - 3-Aminobenzamide

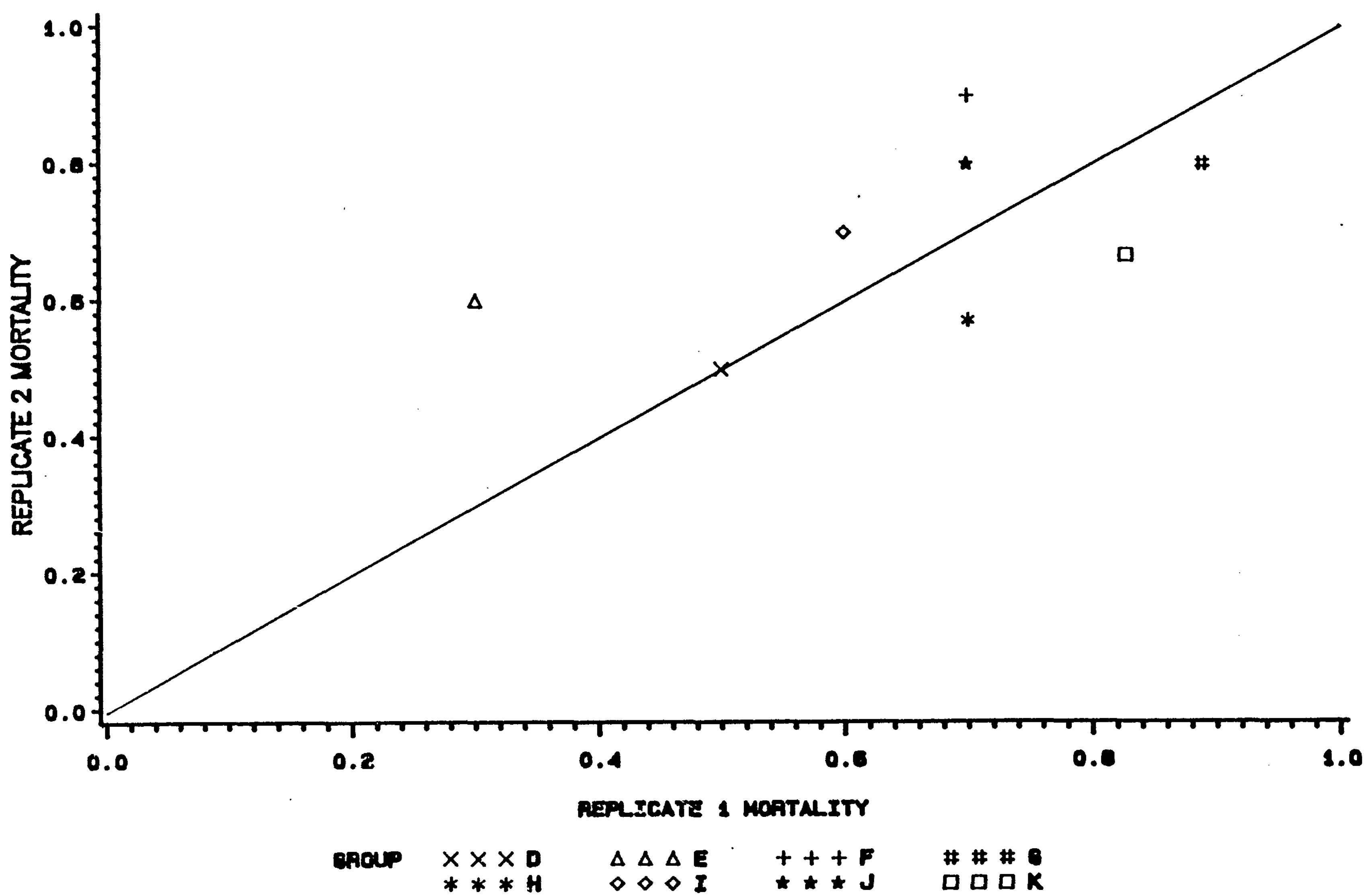


FIGURE 3.41. COMPARISON OF MORTALITY AMONG HD-DOSED GROUPS ACROSS REPLICATES

Target HD Dose - LD_{60} of HD   Inhibitor - Nicotinic Acid

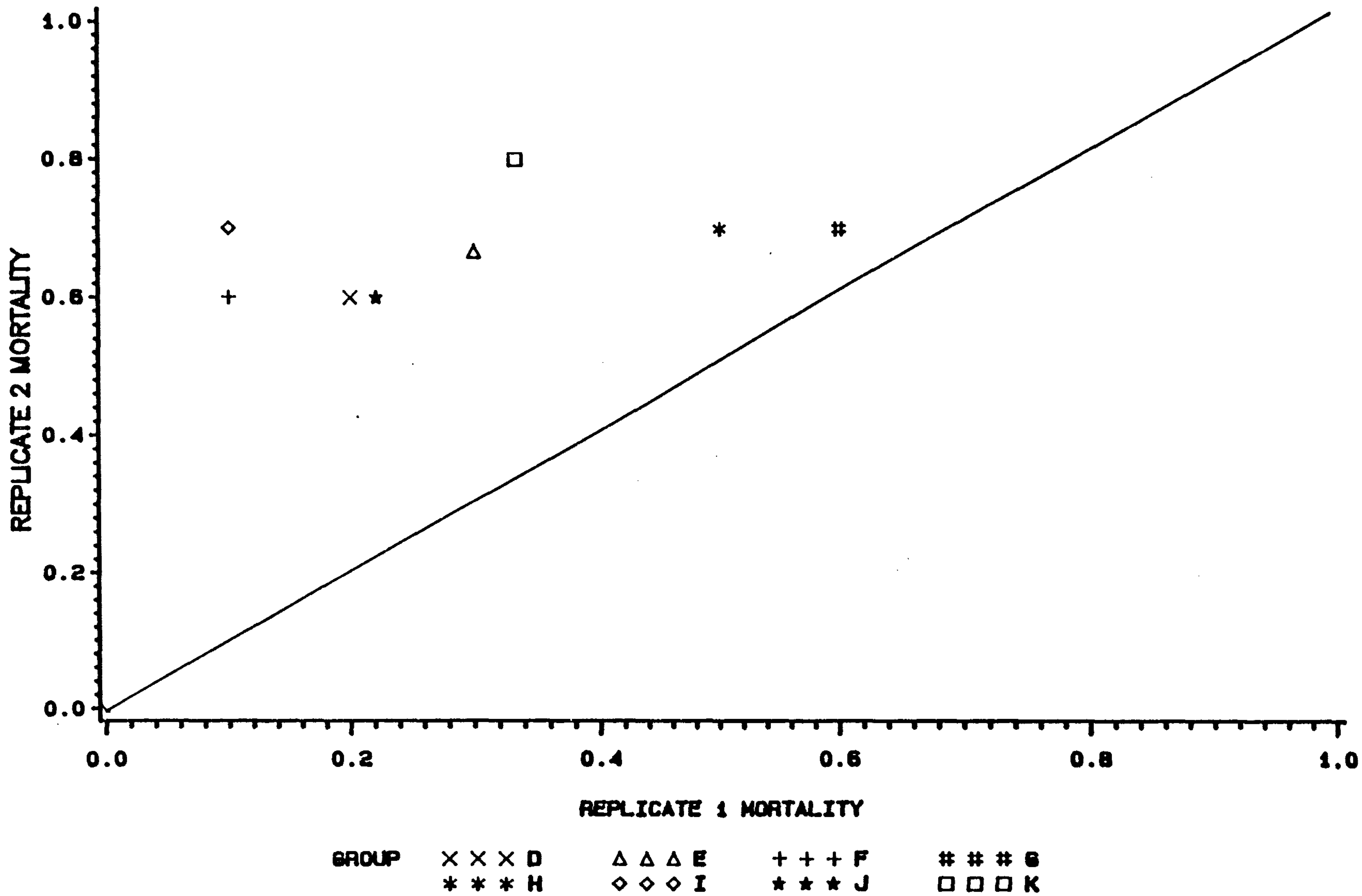


FIGURE 3.42. COMPARISON OF MORTALITY AMONG HD-DOSED GROUPS ACROSS REPLICATES

Target HD Dose - LD_{60} of HD Inhibitor - Nicotinamide

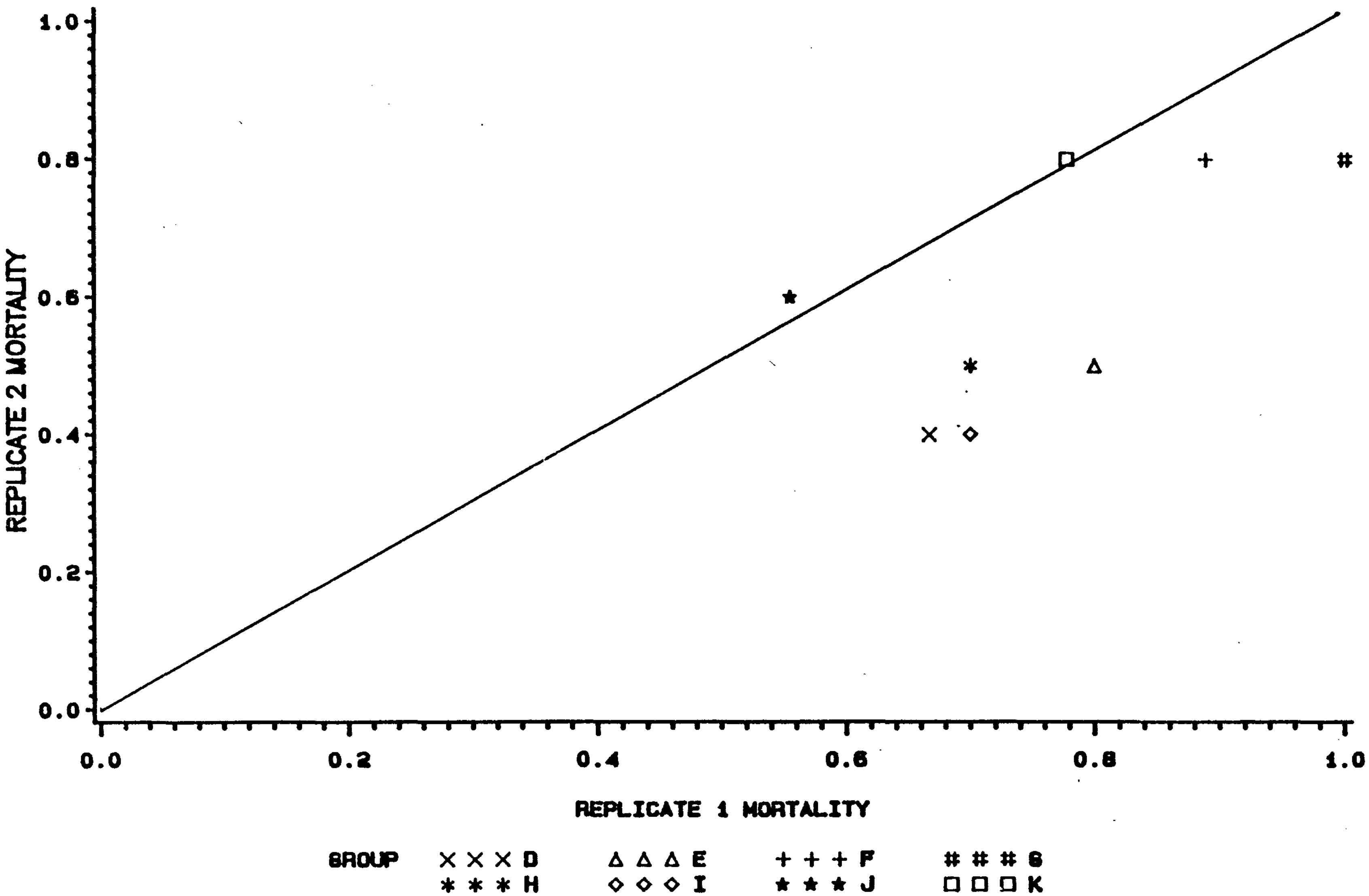


FIGURE 3.43. PERCENT MORTALITY VERSUS TOTAL AMOUNT OF INHIBITOR ADMINISTERED FOR INHIBITOR = 3-AMINOBENZAMIDE, BOTH REPLICATES

Target HD Dose - LD_{30}

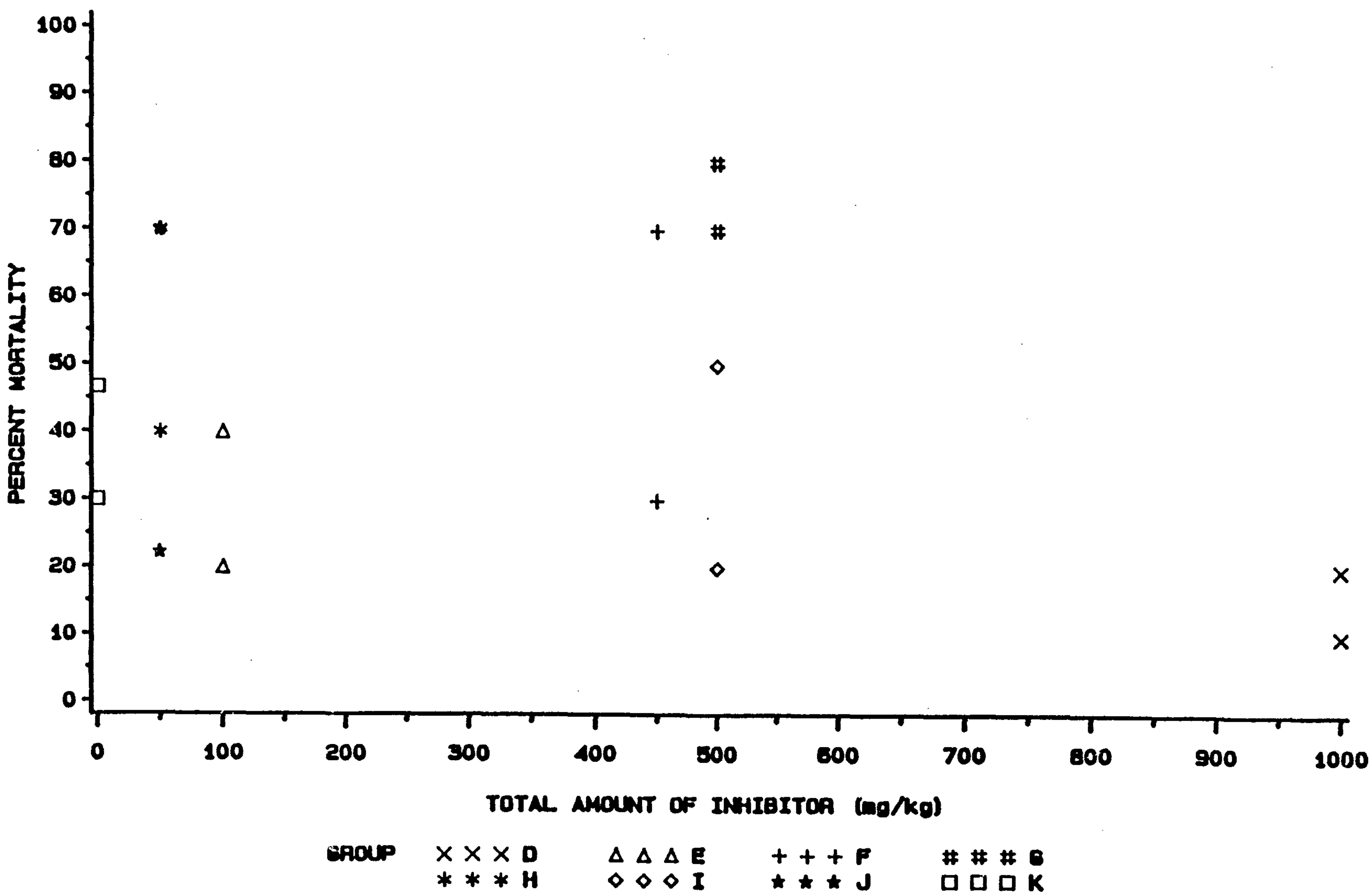


FIGURE 3.44. PERCENT MORTALITY VERSUS TOTAL AMOUNT OF INHIBITOR ADMINISTERED FOR INHIBITOR = NICOTINAMIDE, BOTH REPLICATES

Target HD Dose - LD_{30}

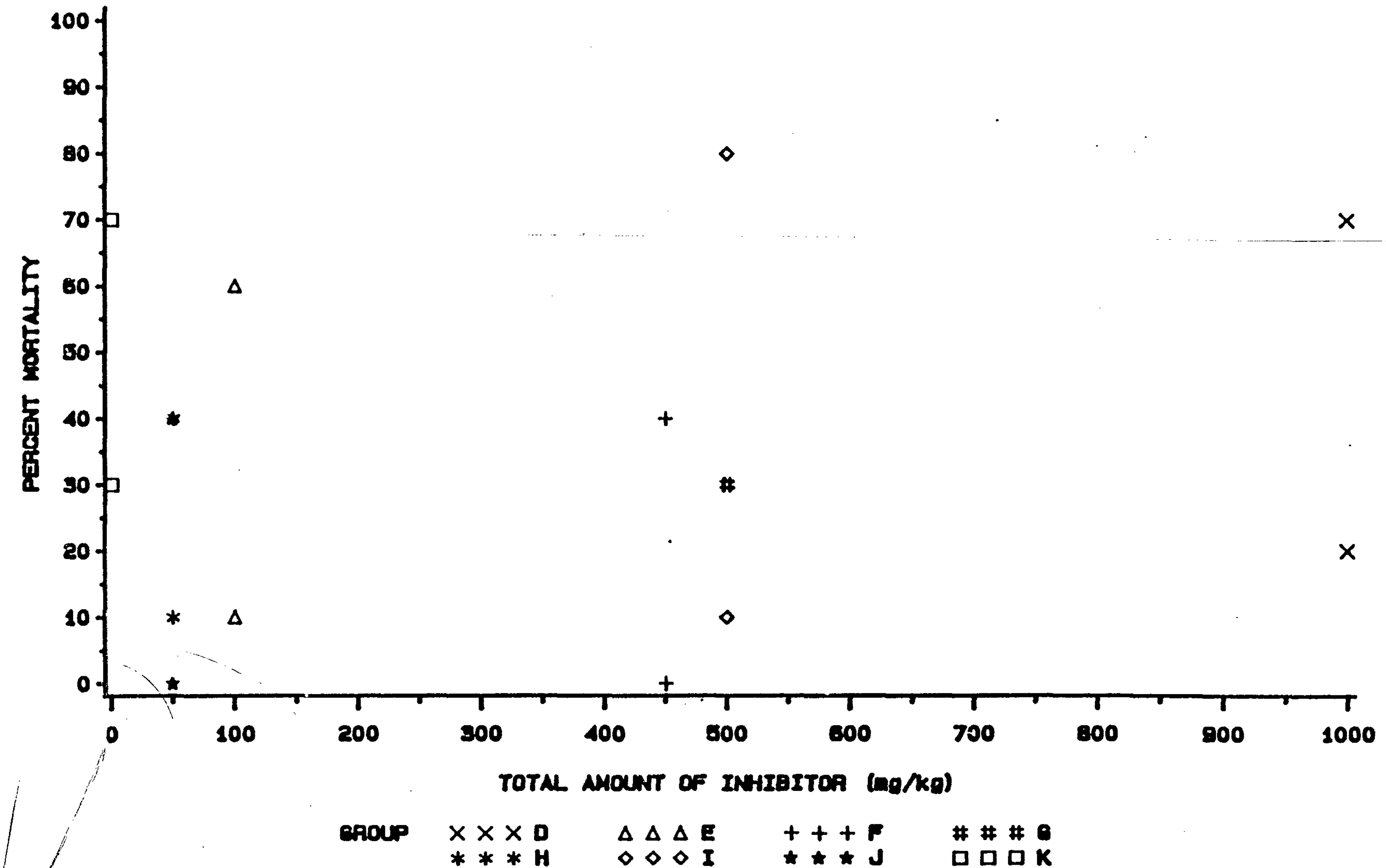


FIGURE 3.45. PERCENT MORTALITY VERSUS TOTAL AMOUNT OF INHIBITOR ADMINISTERED FOR INHIBITOR = NICOTINIC ACID, BOTH REPLICATES

Target HD Dose - LD_{30}

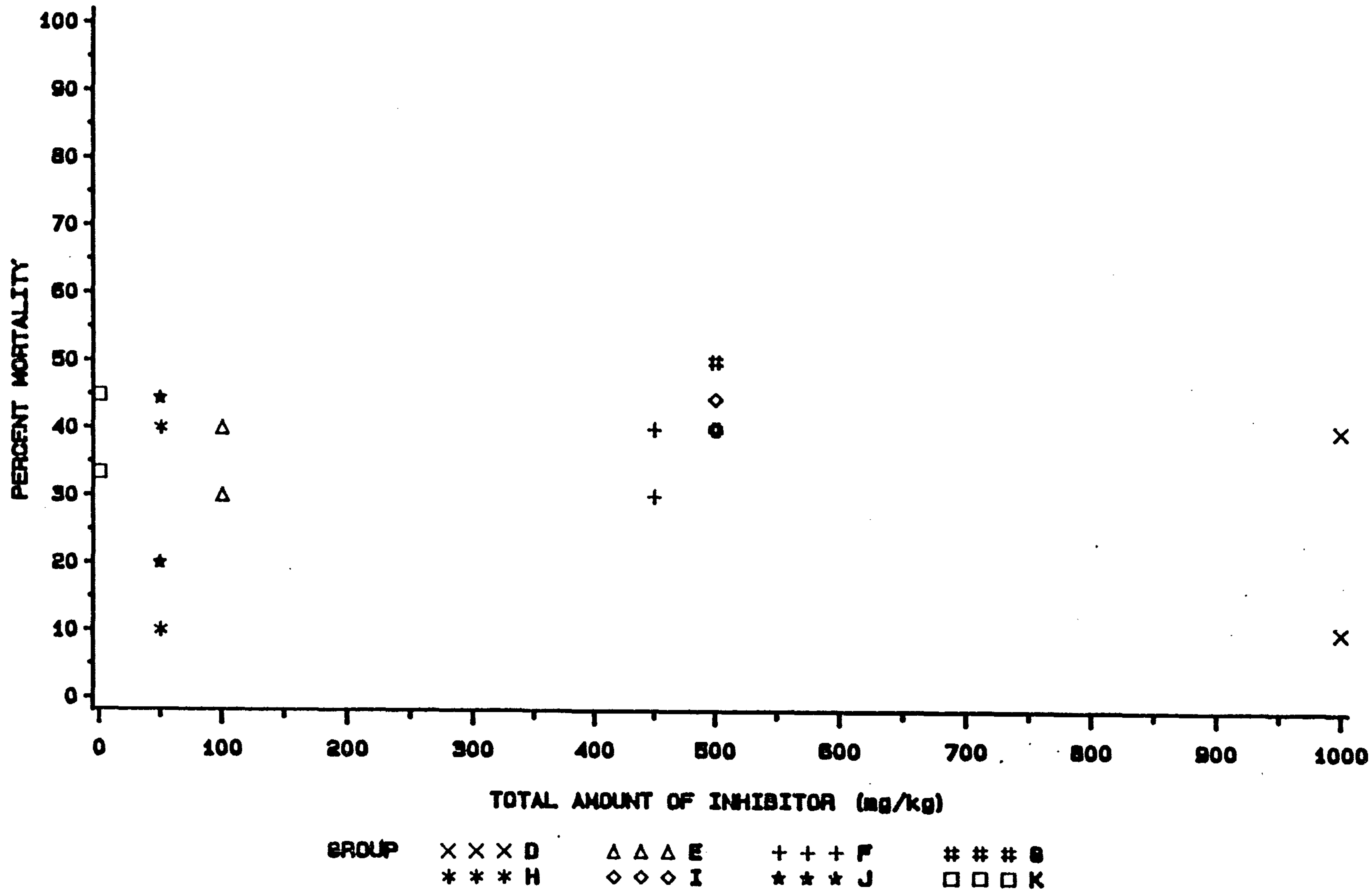


FIGURE 3.46. PERCENT MORTALITY VERSUS TOTAL AMOUNT OF INHIBITOR ADMINISTERED FOR INHIBITOR = 3-AMINOBENZAMIDE, BOTH REPLICATES

Target HD Dose - LD_{60}

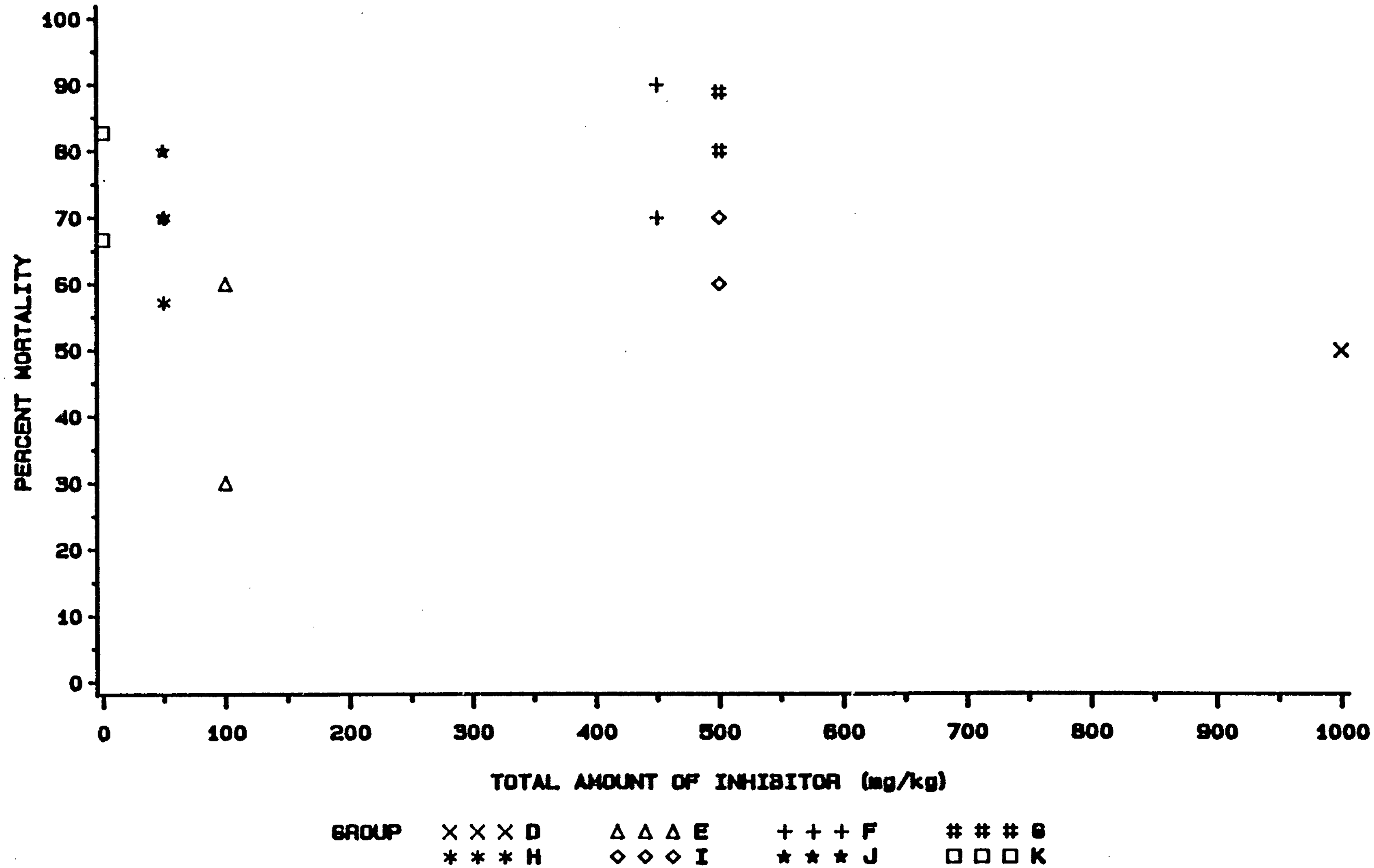


FIGURE 3.47. PERCENT MORTALITY VERSUS TOTAL AMOUNT OF INHIBITOR ADMINISTERED FOR INHIBITOR = NICOTINAMIDE, BOTH REPLICATES

Target HD Dose LD_{60}

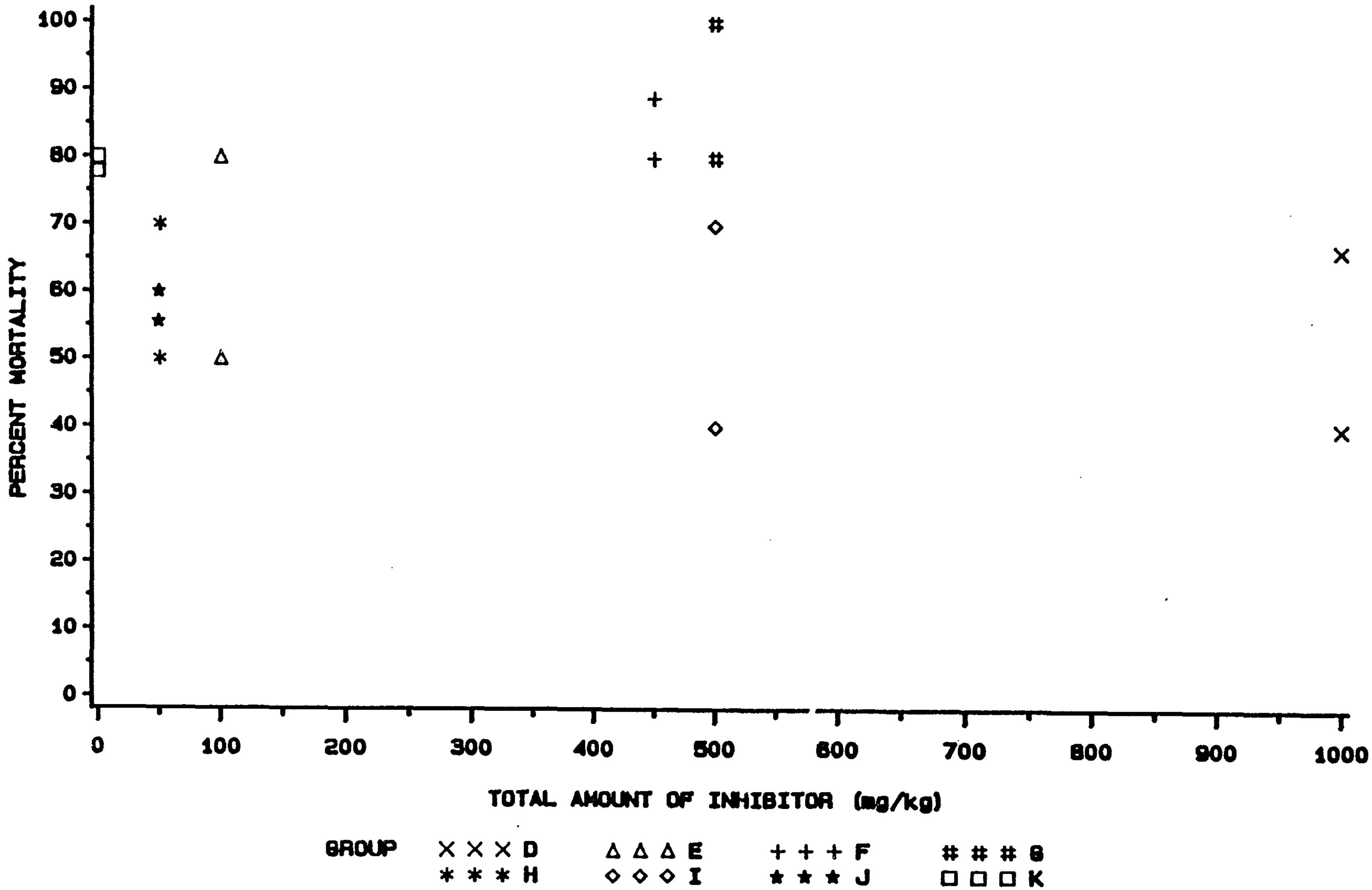


FIGURE 3.48. PERCENT MORTALITY VERSUS TOTAL AMOUNT OF INHIBITOR ADMINISTERED FOR INHIBITOR = NICOTINIC ACID, BOTH REPLICATES

Target HD Dose LD_{60}

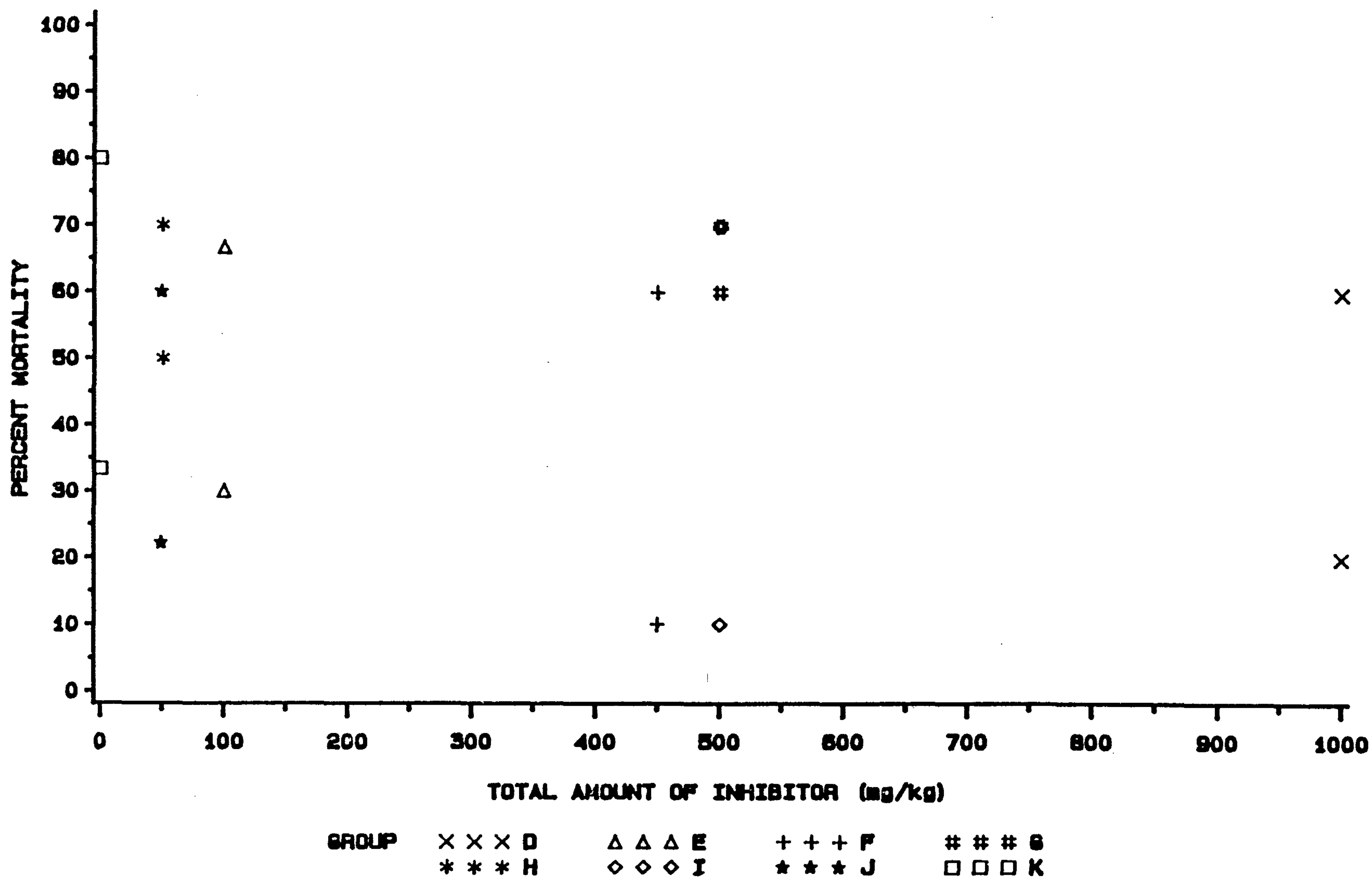


FIGURE 3.49. WHITE BLOOD CELL (WBC) COUNT FOR INHIBITOR = NICOTINAMIDE AMONG NO-HD CONTROL GROUPS

Target HD Dose - LD_{30}

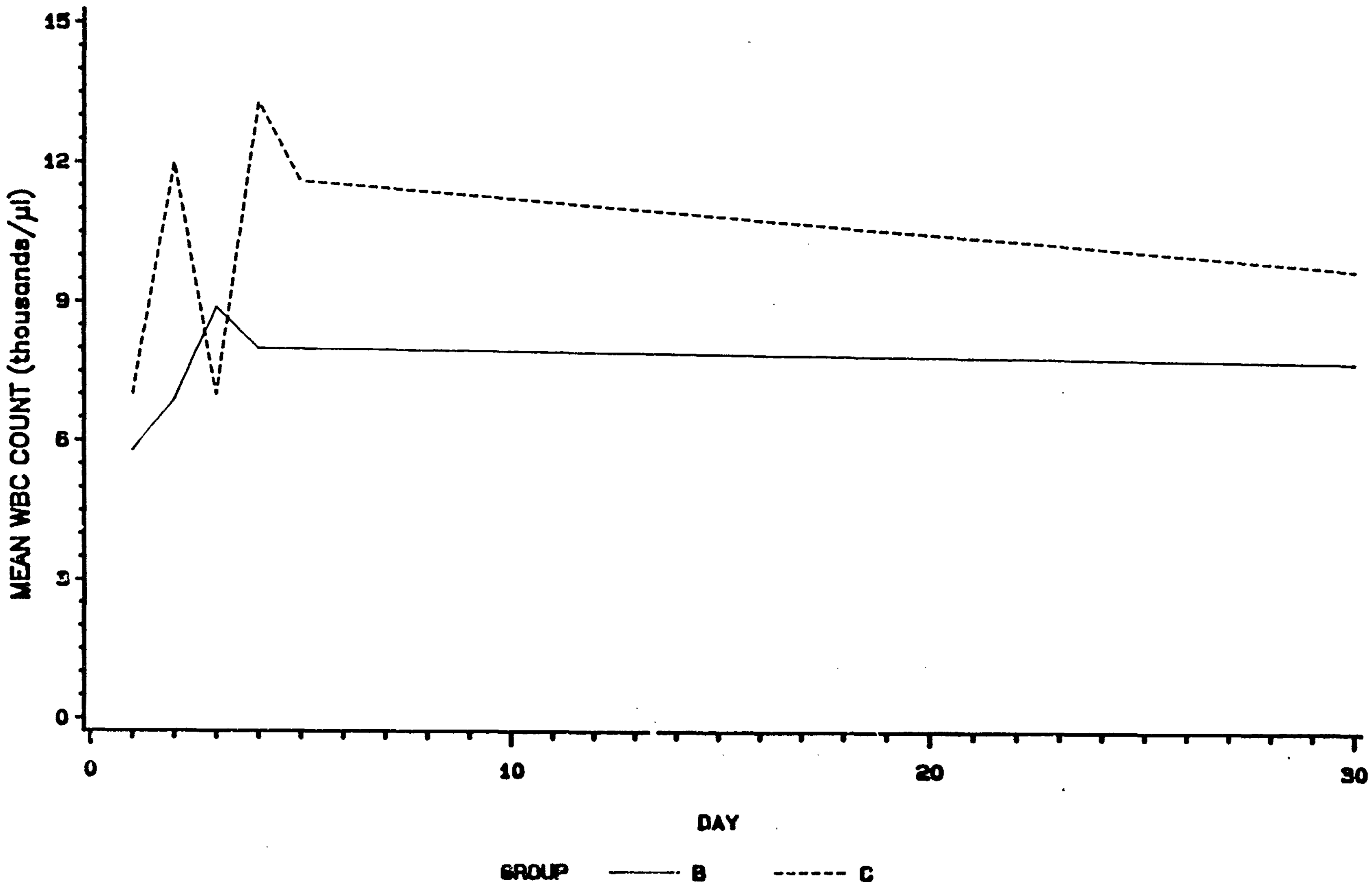


FIGURE 3.50. WHITE BLOOD CELL (WBC) COUNT FOR INHIBITOR = NICOTINAMIDE AMONG NO-HD CONTROL GROUPS

Target HD Dose - LD_{60}

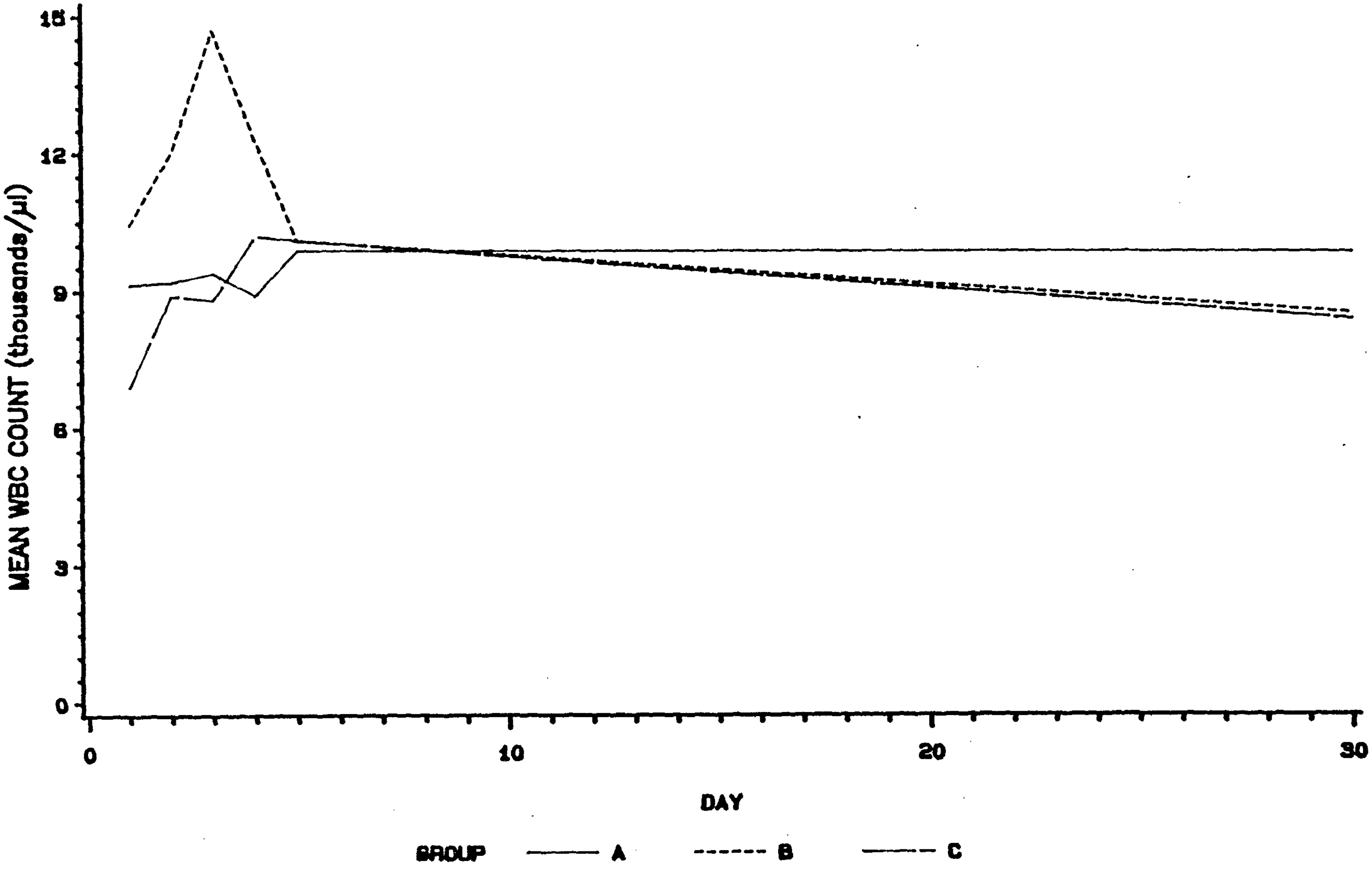


FIGURE 3.51. WHITE BLOOD CELL (WBC) COUNT FOR INHIBITOR = NICOTINIC ACID AMONG NO-HD CONTROL GROUPS

Target HD Dose - LD_{30}

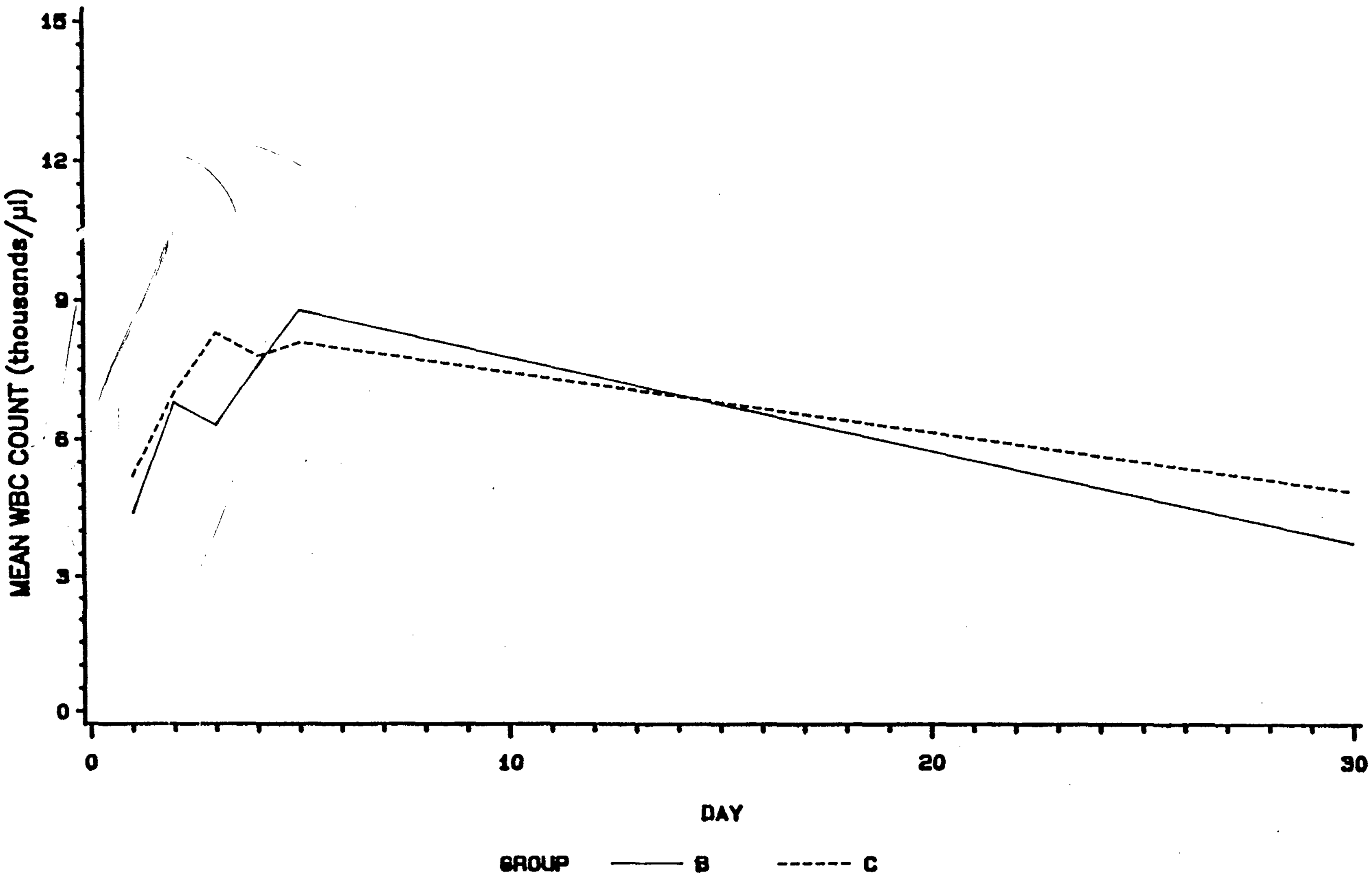


FIGURE 3.52. WHITE BLOOD CELL (WBC) COUNT FOR INHIBITOR = NICOTINIC ACID AMONG NO-HD CONTROL GROUPS

Target HD Dose - LD_{60}

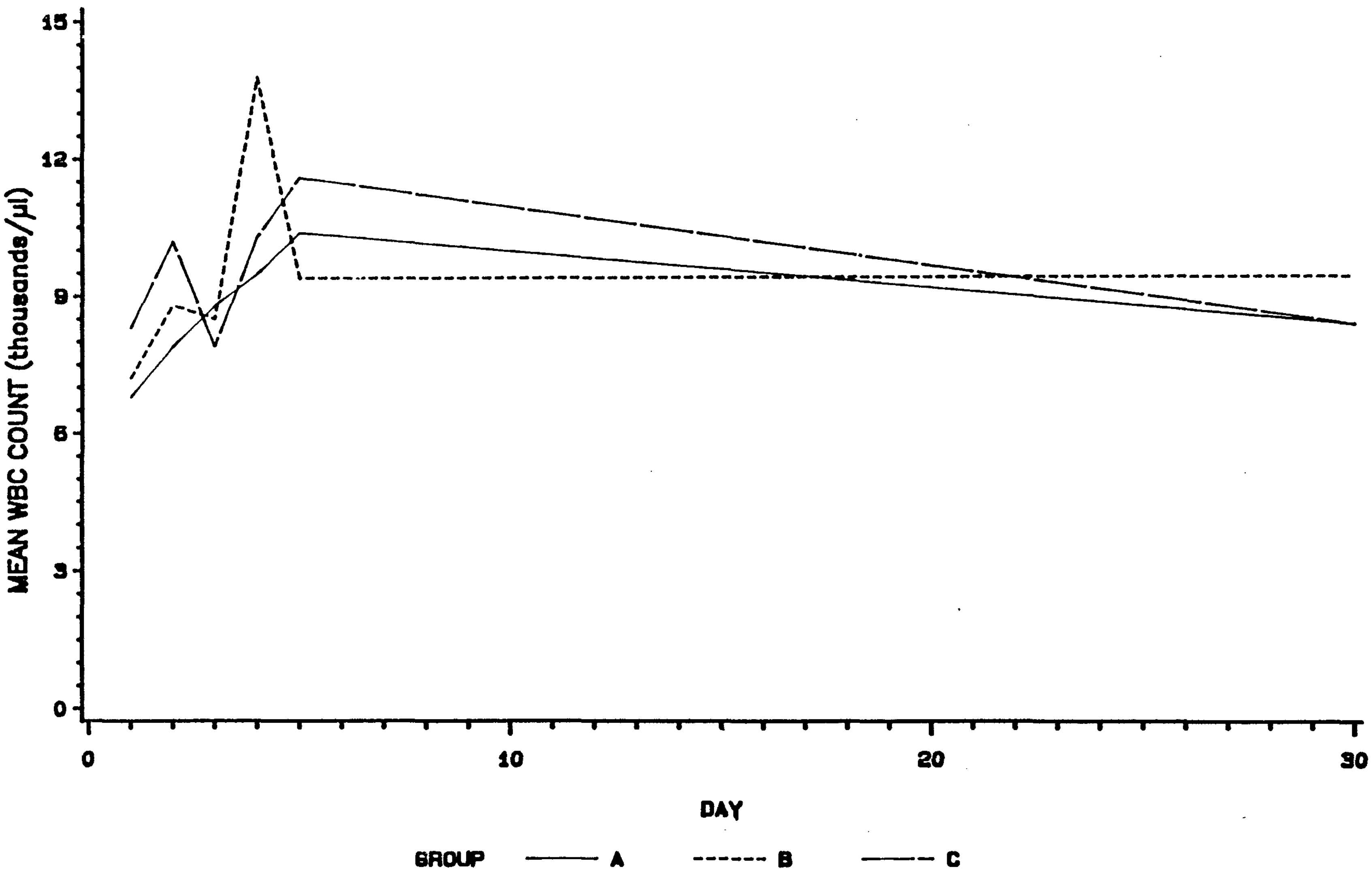


FIGURE 3.53. ABSOLUTE LYMPHOCYTE COUNT FOR INHIBITOR = 3-AMINOBENZAMIDE AMONG NO-HD CONTROL GROUPS

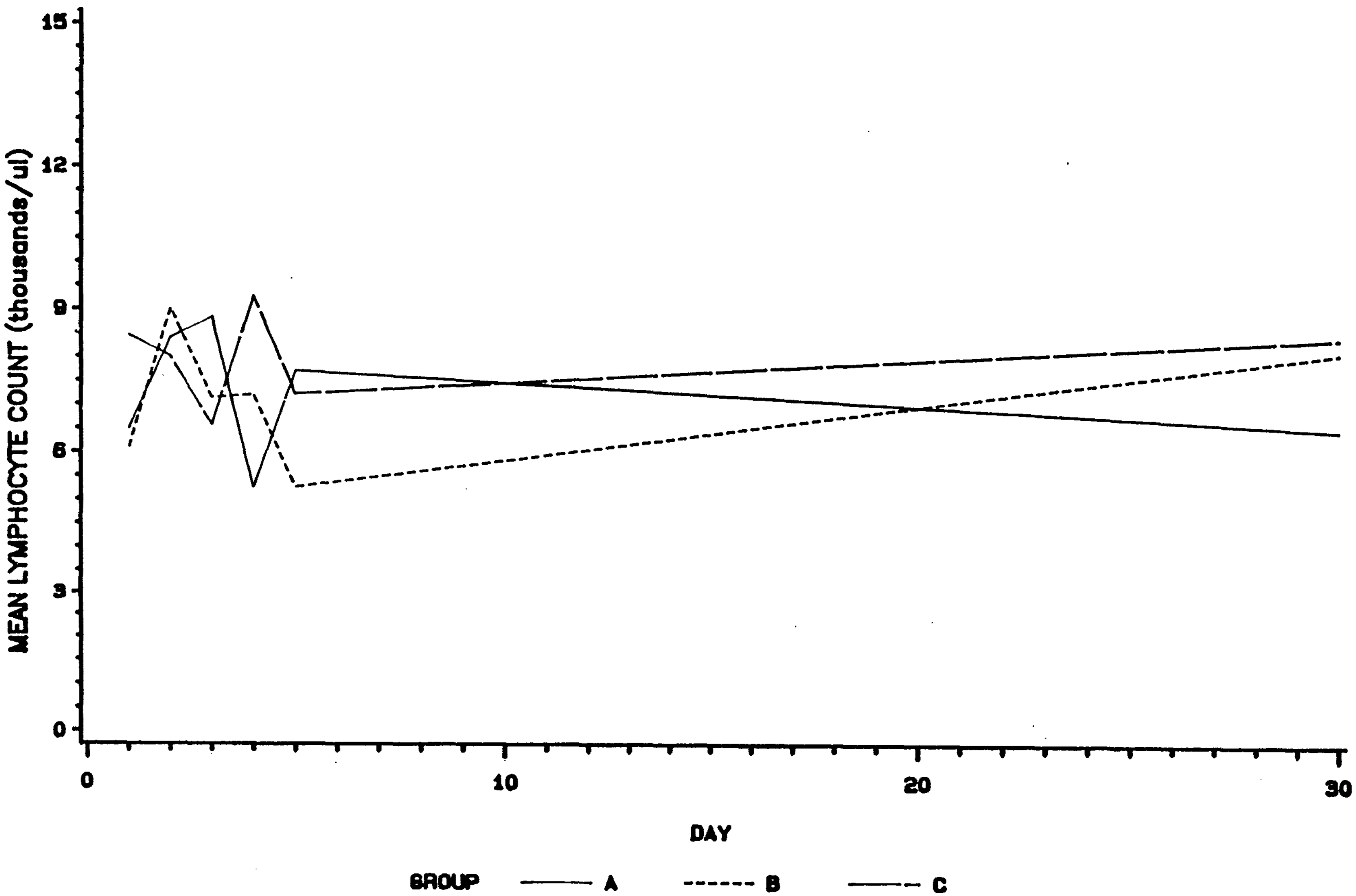


FIGURE 3.54. GROUP K WHITE BLOOD CELL (WBC) COUNT FOR ALL INHIBITORS, BOTH REPLICATES

Target HD Dose - LD_{30}

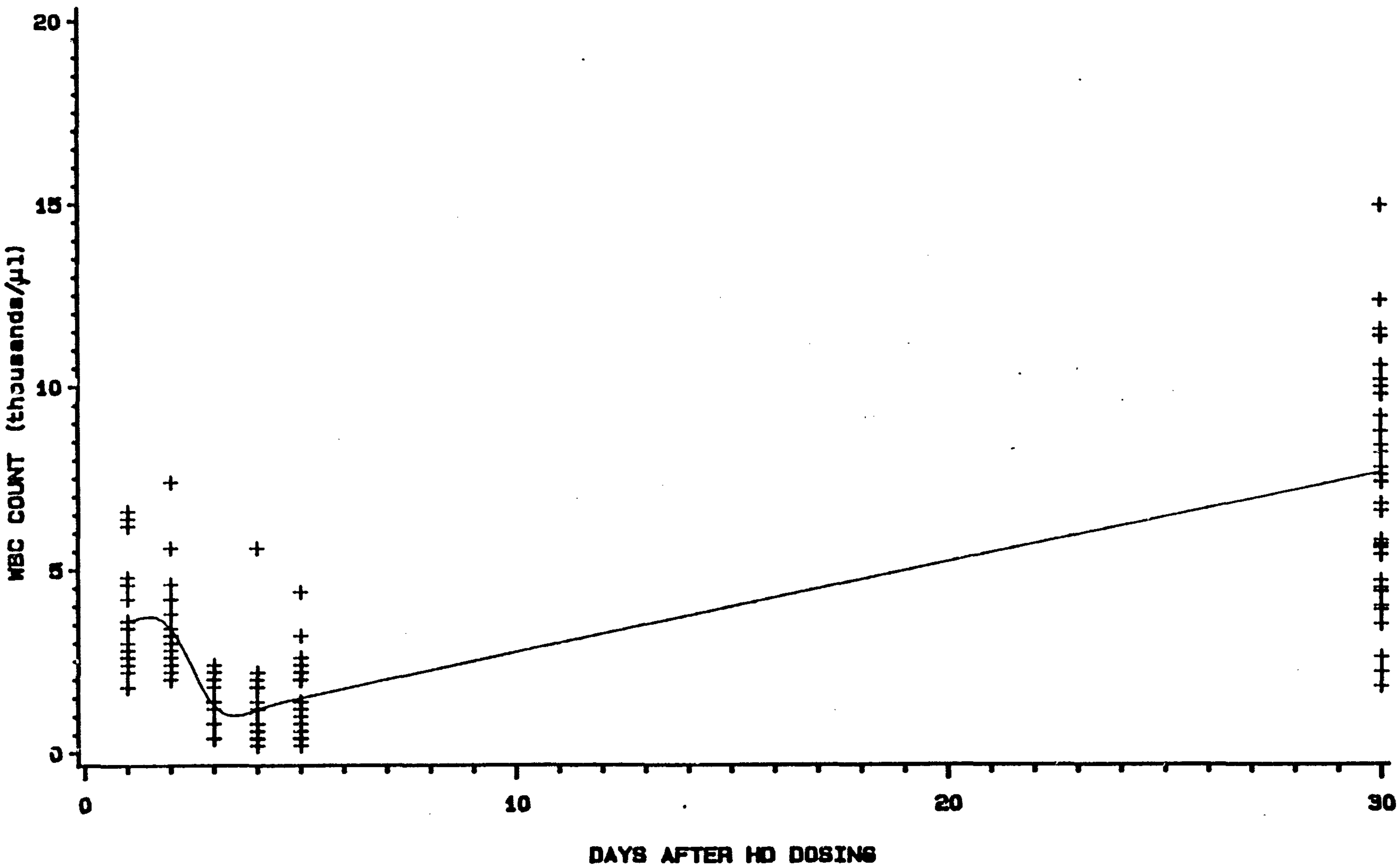


FIGURE 3.55. GROUP K WHITE BLOOD CELL (WBC) COUNT FOR ALL INHIBITORS, BOTH REPLICATES

Target HD Dose - LD_{60}

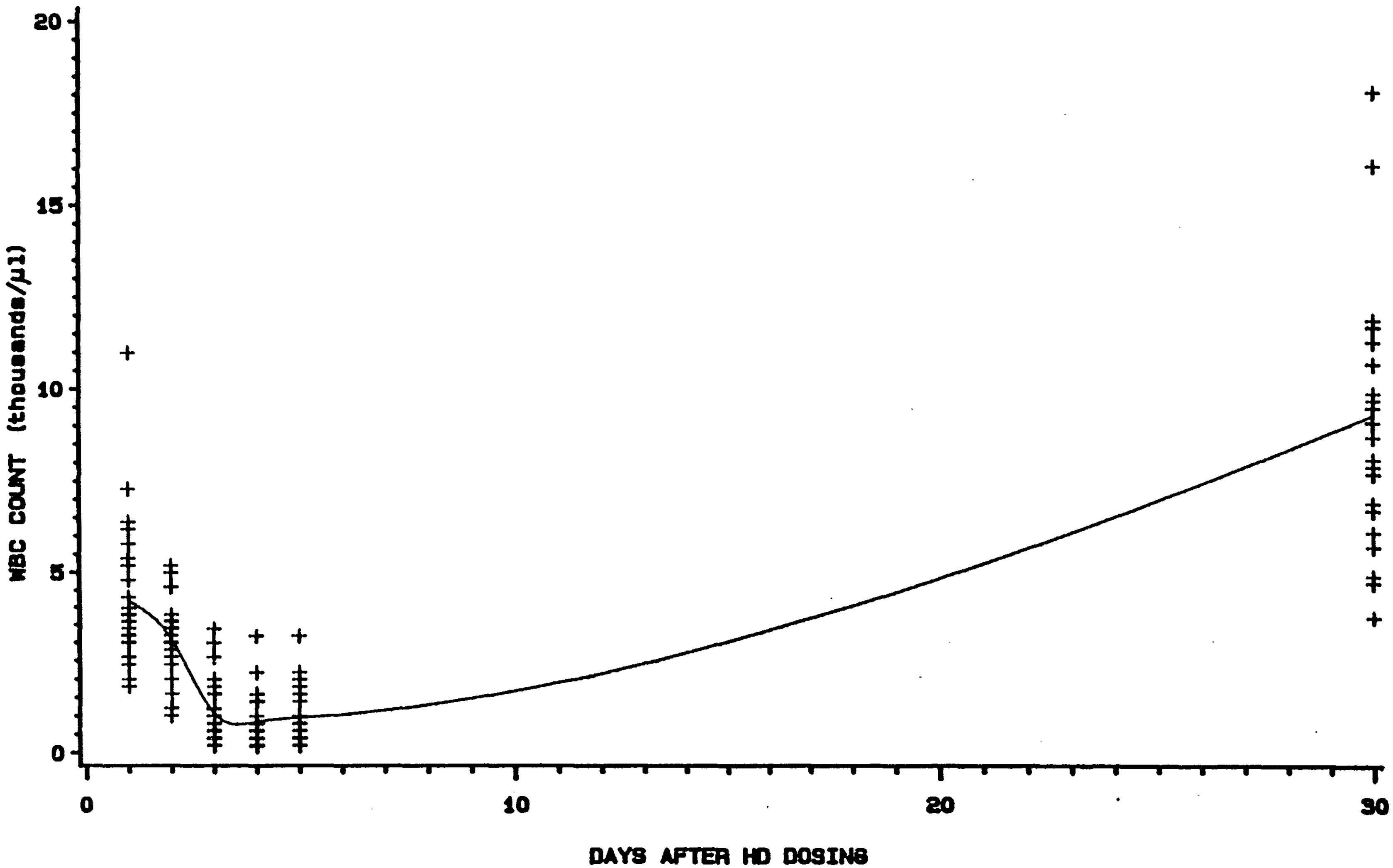


FIGURE 3.56. GROUP K LYMPHOCYTE COUNT FOR ALL INHIBITORS, BOTH REPLICATES

Target HD Dose - LD_{30}

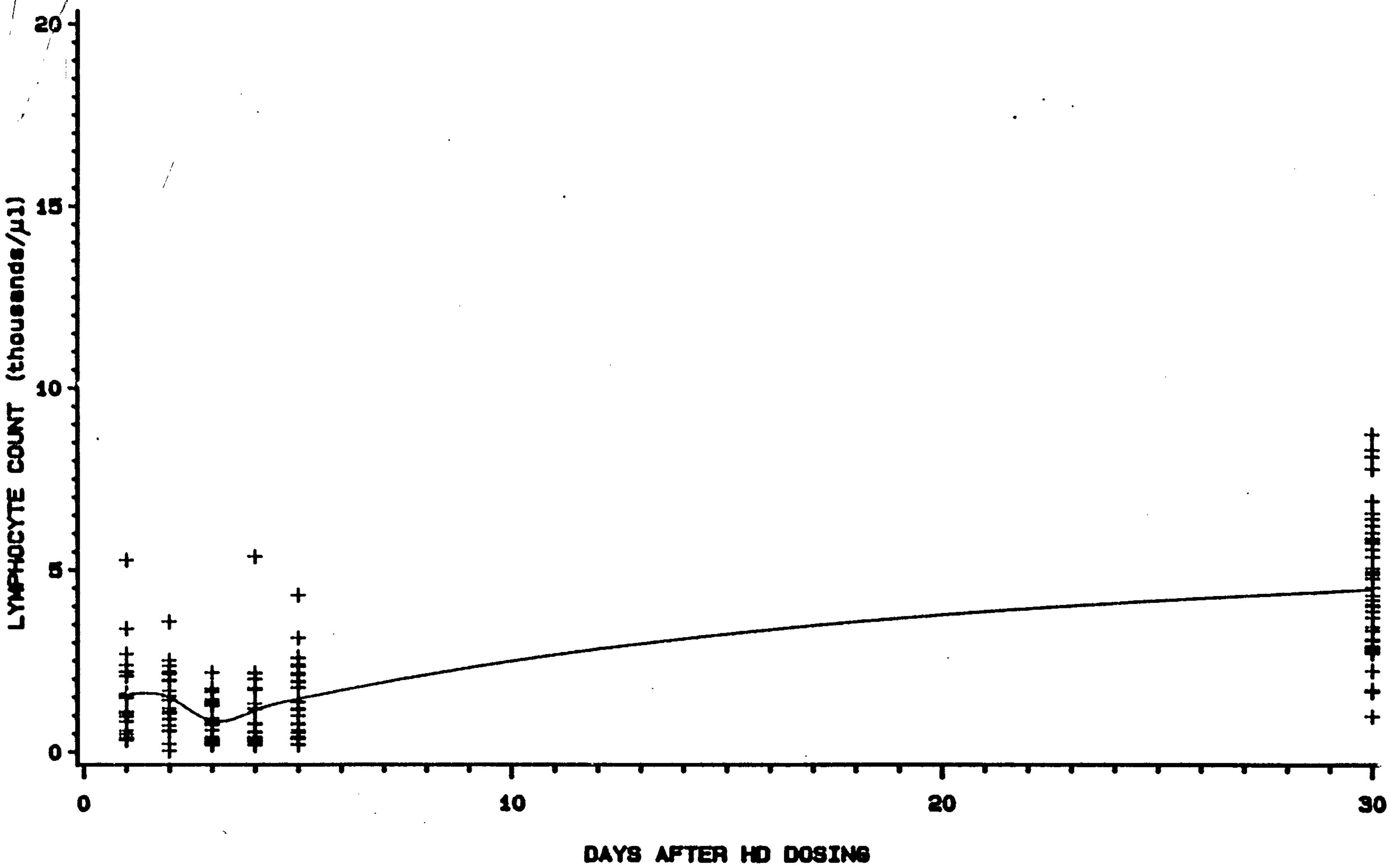


FIGURE 3.57. GROUP K LYMPHOCYTE COUNT FOR ALL INHIBITORS, BOTH REPLICATES

Target HD Dose - LD_{60}

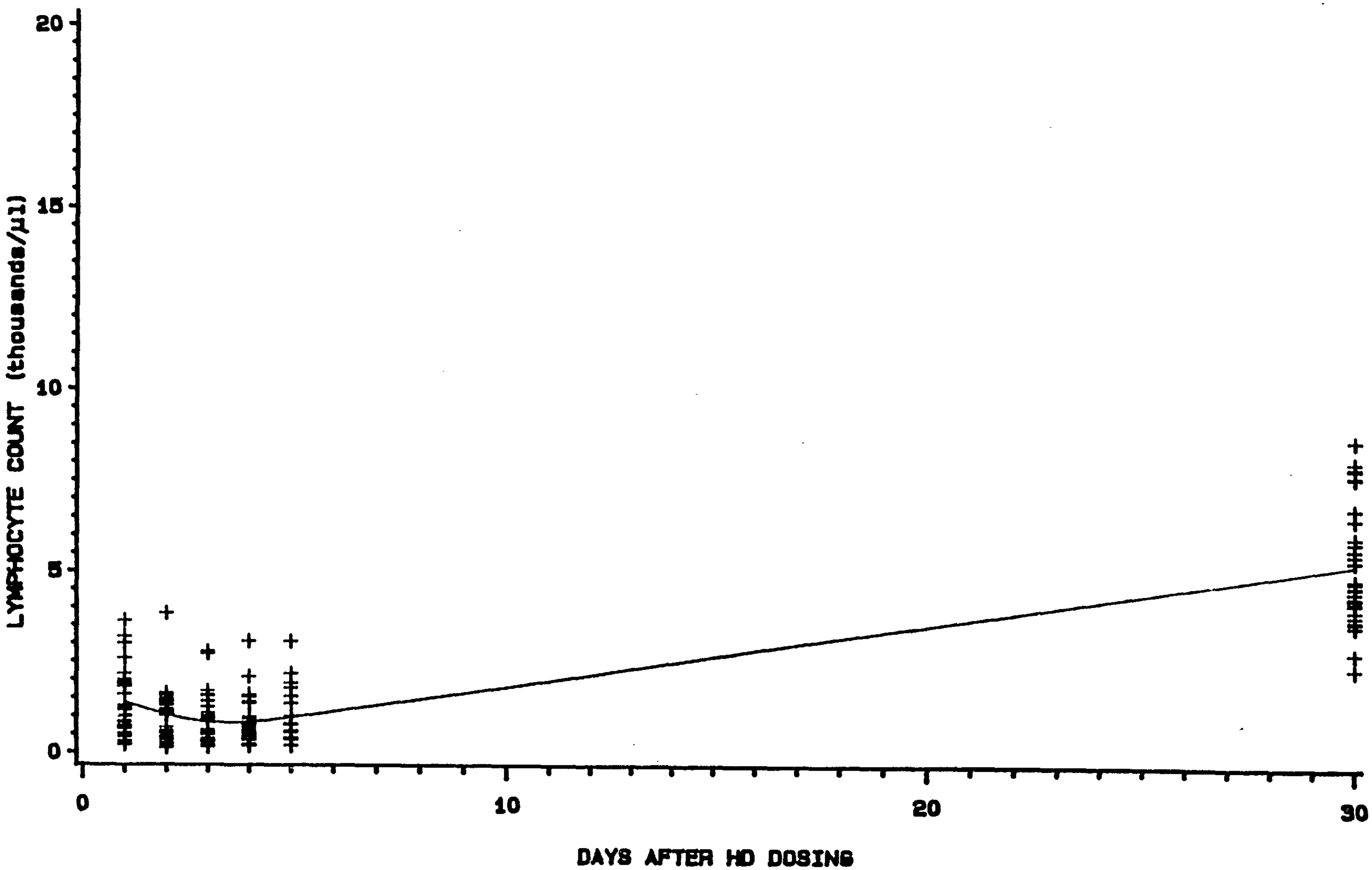


FIGURE 3.58. GROUP K SEGMENTED NEUTROPHIL COUNT FOR ALL INHIBITORS, BOTH REPLICATES

Target HD Dose - LD_{30}

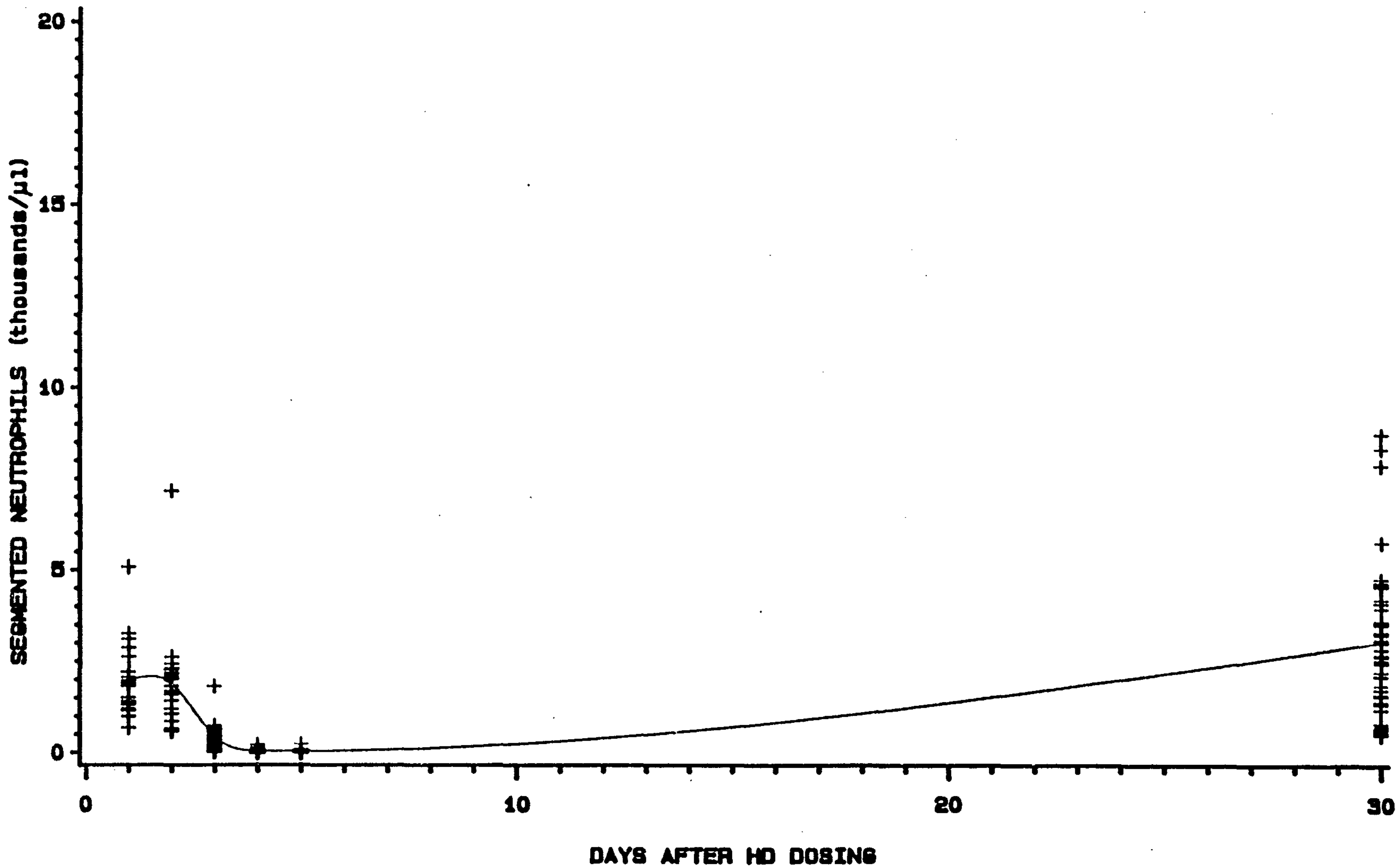


FIGURE 3.59. GROUP K SEGMENTED NEUTROPHIL COUNT FOR ALL INHIBITORS, BOTH REPLICATES

Target HD Dose - LD_{60}

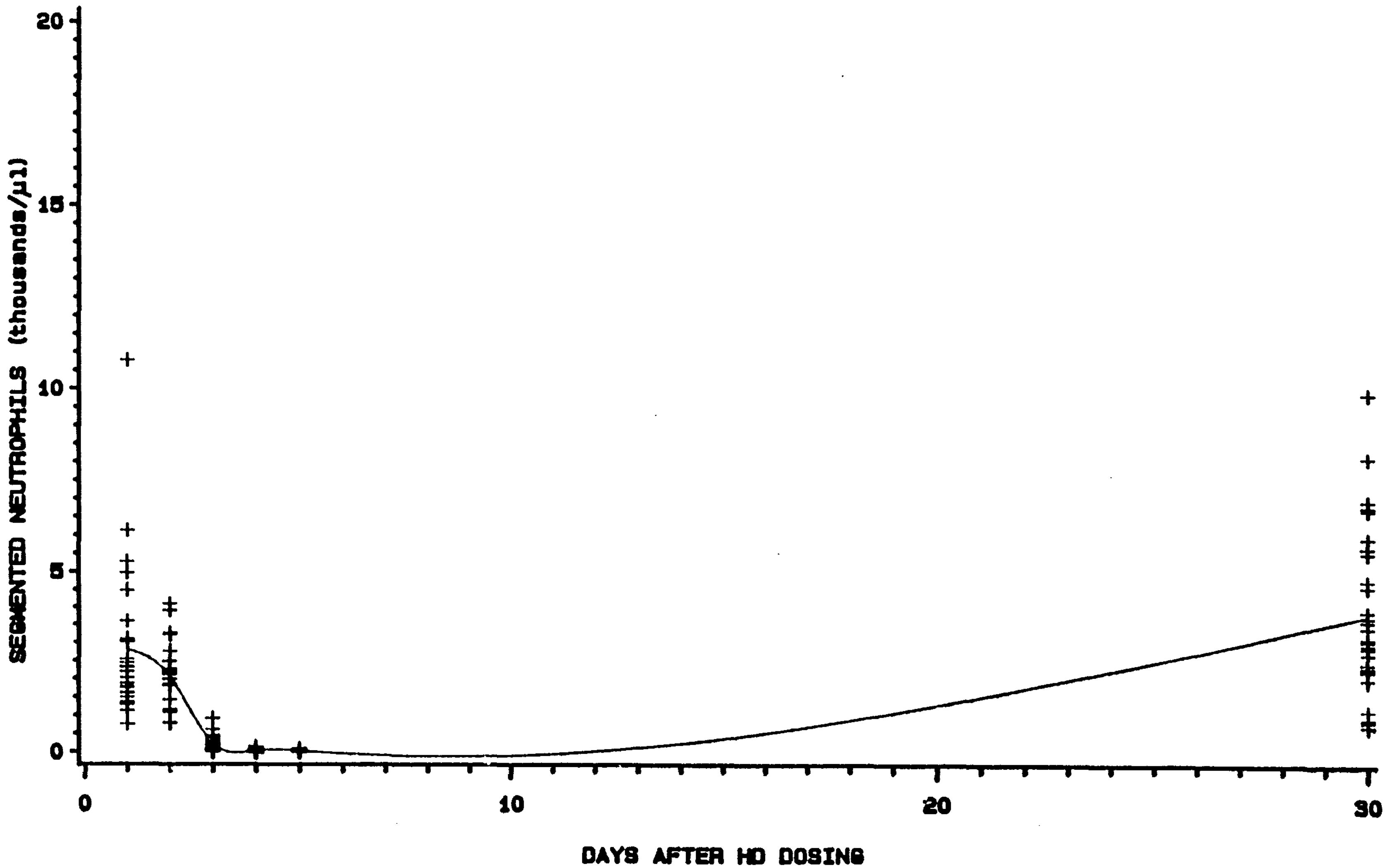


FIGURE 3.60. WHITE BLOOD CELL (WBC) COUNT FOR TARGET HD DOSE = LD_{60}, INHIBITOR = NICOTINIC ACID, BOTH REPLICATES

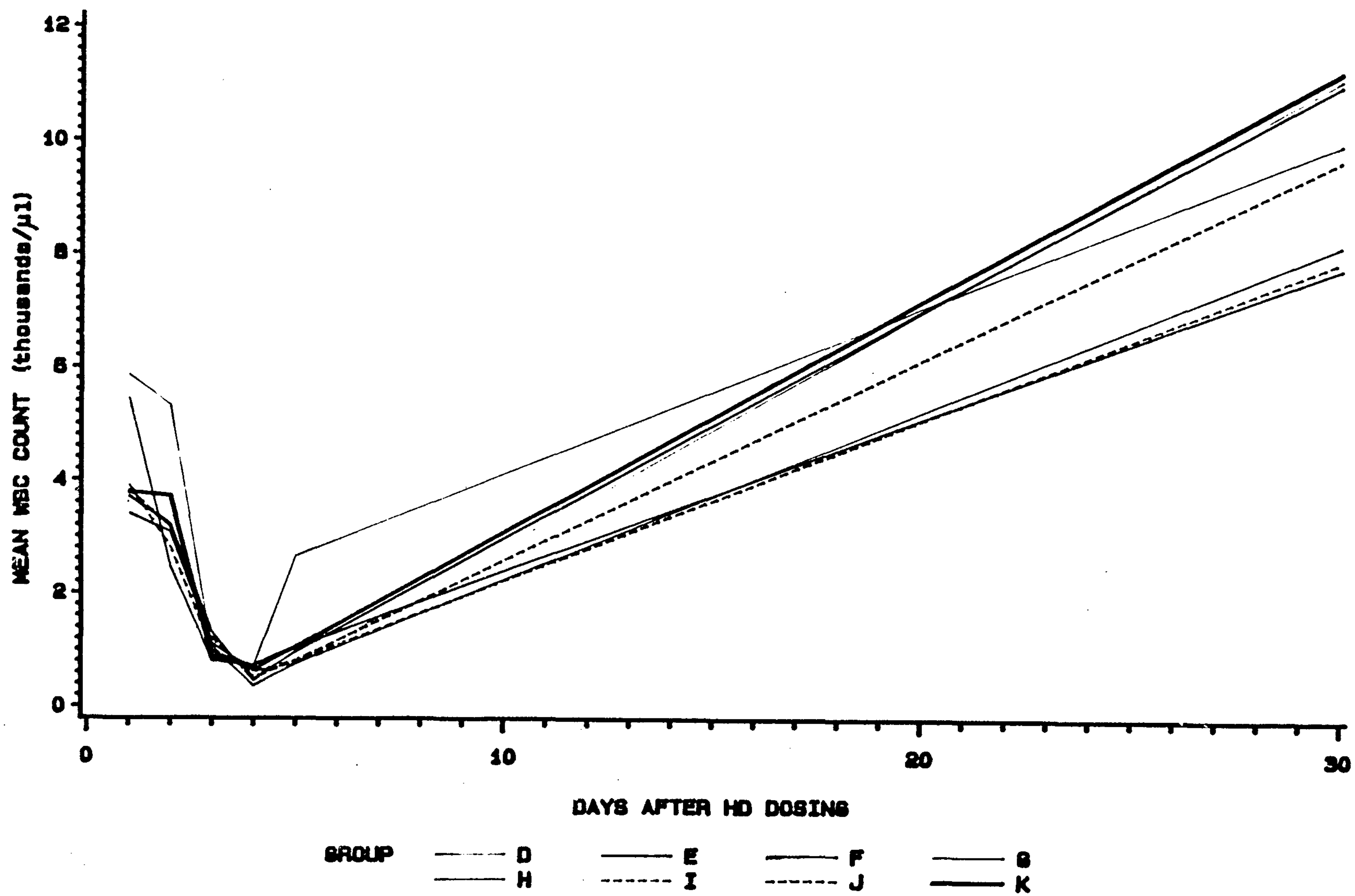


FIGURE 3.61. SEGMENTED NEUTROPHIL COUNT FOR TARGET HD DOSE = LD_{60}, INHIBITOR = NICOTINIC ACID, BOTH REPLICATES

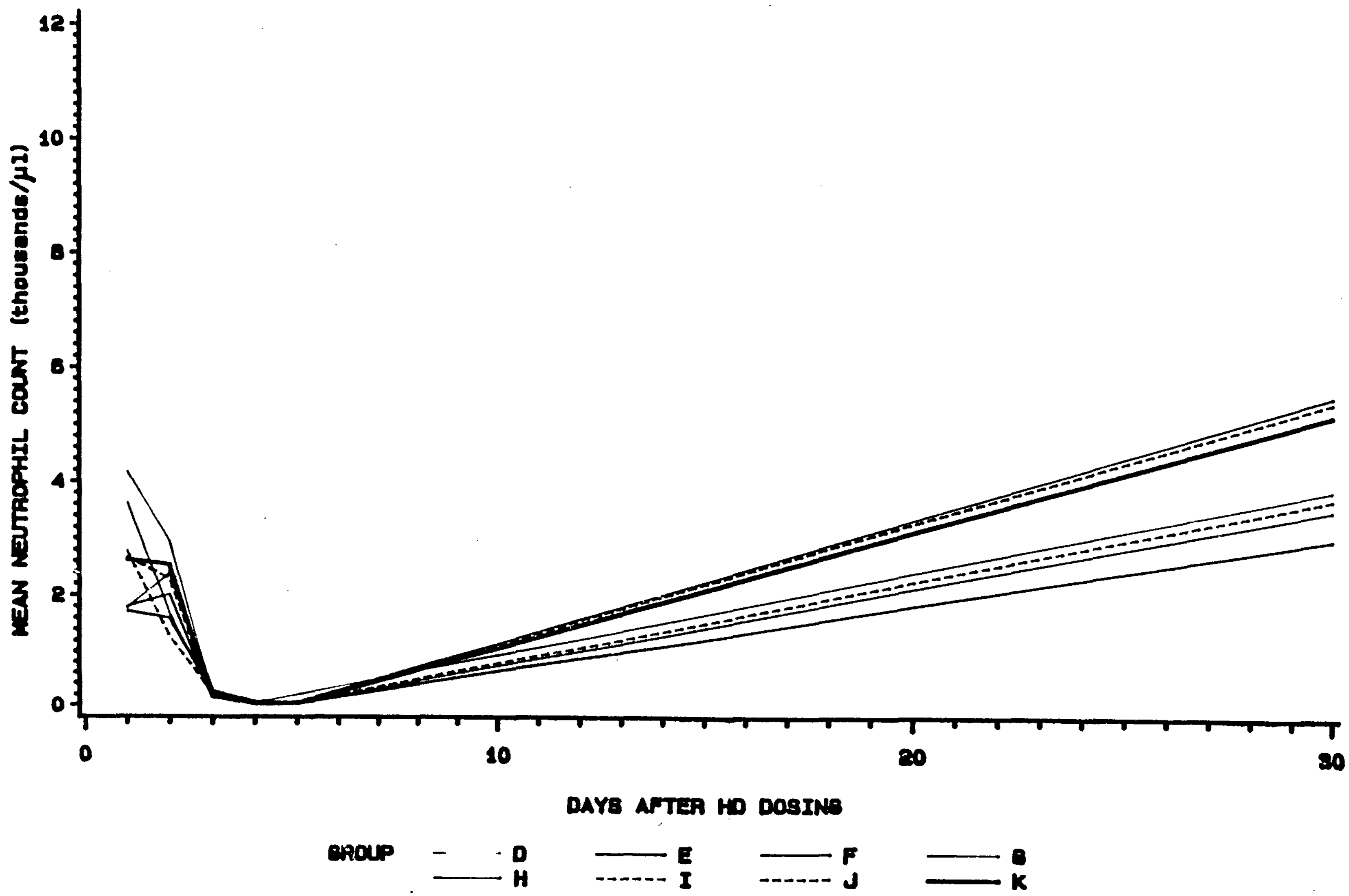


FIGURE 3.62. LYMPHOCYTE COUNT FOR TARGET HD DOSE = LD_{30}, INHIBITOR = NICOTINAMIDE, BOTH REPLICATES

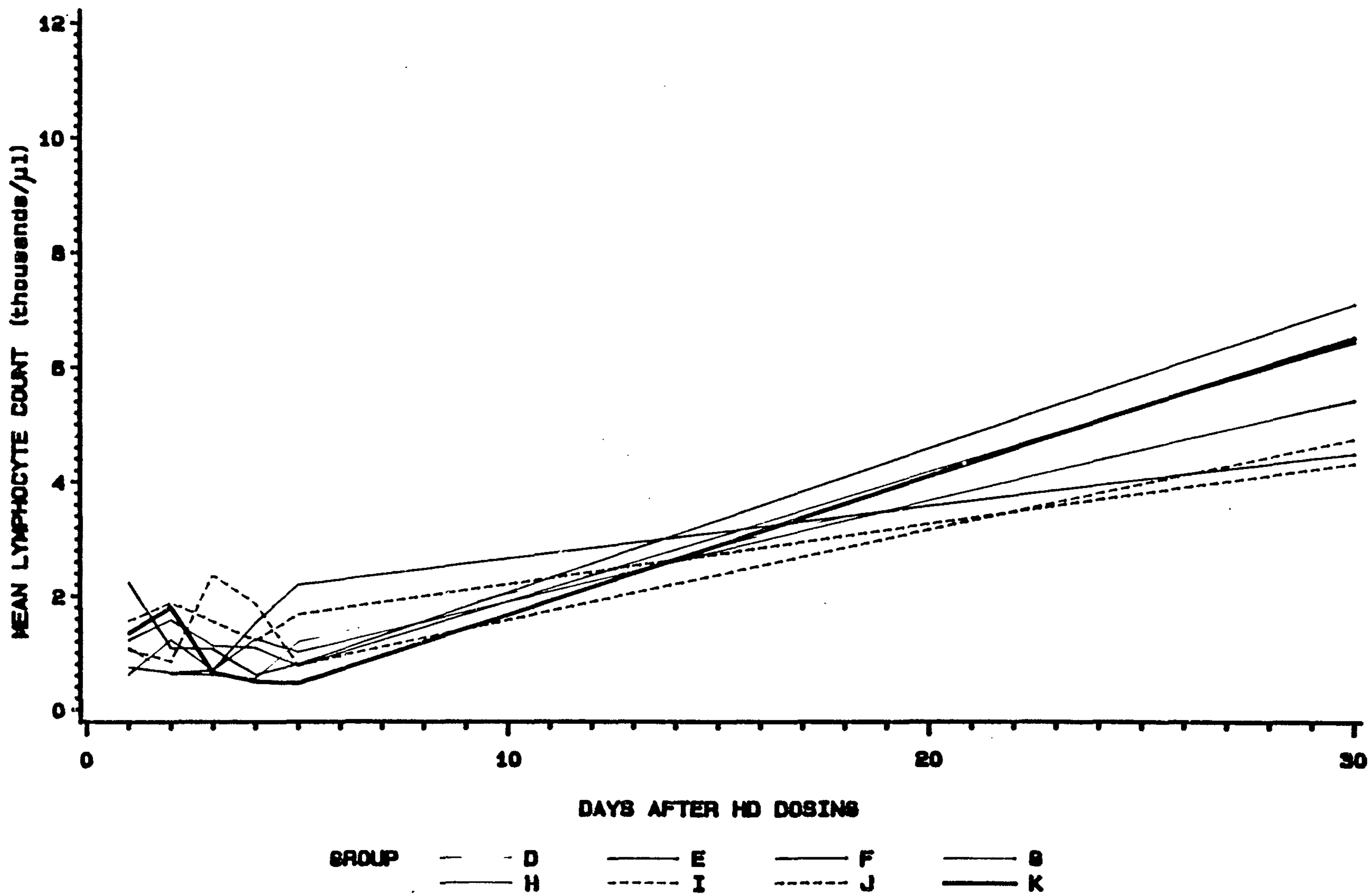
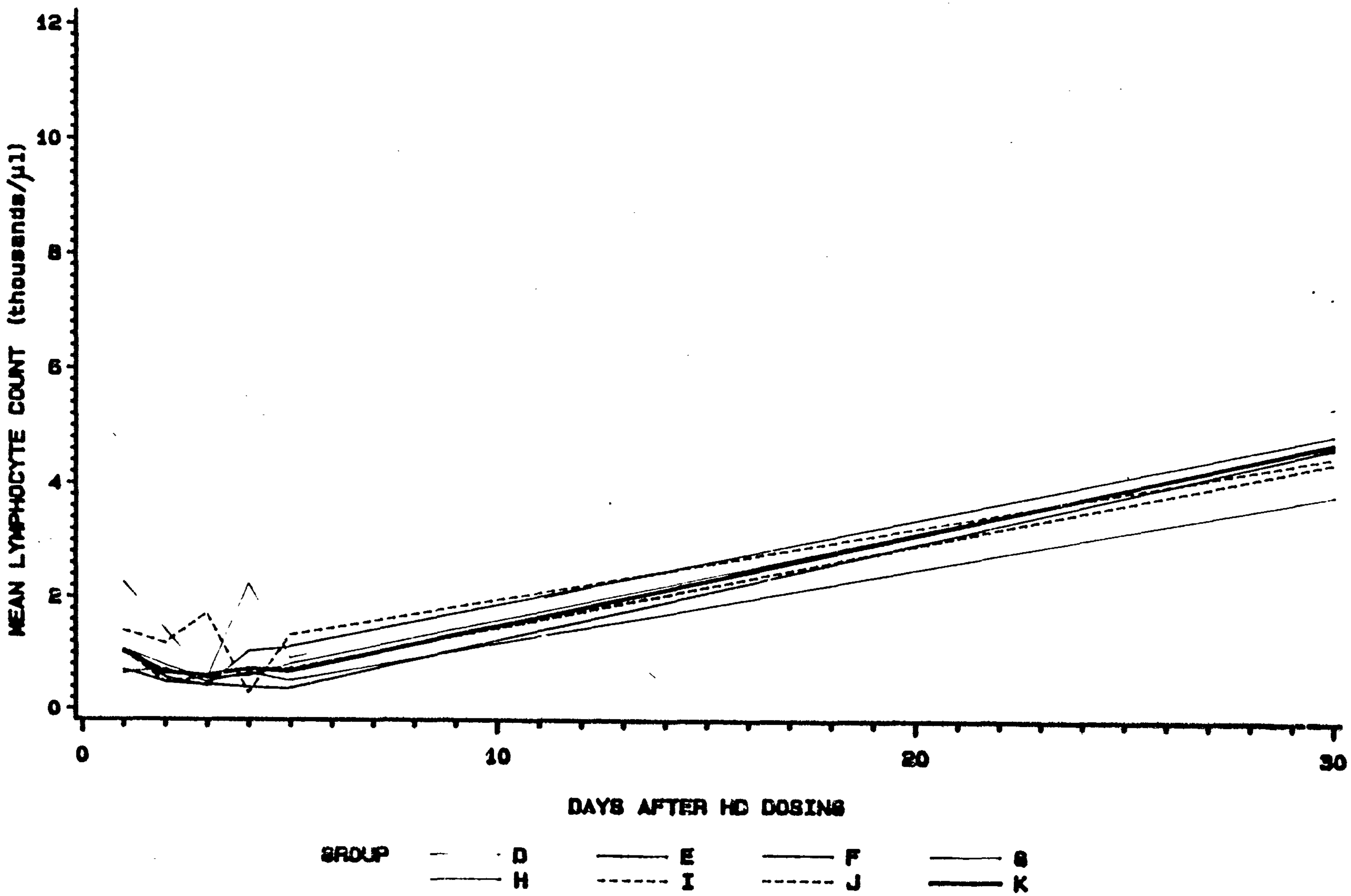


FIGURE 3.63. SEGMENTED LYMPHOCYTE COUNT FOR TARGET HD DOSE = LD_{60}, INHIBITOR = NICOTINAMIDE, BOTH REPLICATES



APPENDIX C

Statistical Method for Comparing Data Between Replicate Studies

Statistical Method for Comparing Data Between Replicate Studies

An 11-parameter multiple regression model was applied to results from each replicate and to the pooled replicates for a given experiment. One degree of freedom (df) was assigned to each of these 11 parameters: intercept, day, day^2, day^3, dose, $dose^2$, $dose^3$, and 4 linear and quadratic interactions. An F test ($\alpha = 0.05$, 2-sided) was applied to the multiple regression model results as follows:

$$F(11,\Sigma df) = \frac{(SS_{pooled} - \Sigma SS)/(df_{pooled} - \Sigma df)}{\Sigma SS/\Sigma df}$$

where $F(11,\Sigma df)$ was the F ratio at 11df (the number of parameters in the model) and Σdf (the sum df of the individual replicates),

SS_{pooled} was the sum of squares from the ANOVA on both replicates,

ΣSS was the total of the sums of squares from the individual replicates,

df_{pooled} was the df associated with the error from the ANOVA on both replicates, and

Σdf was the total df associated with the error from the individual replicates.

APPENDIX D

Statistical Method for Analysis of Results from Inhibitor Studies

Statistical Method for Analysis of Results from Inhibitor Studies

Mortality Data

Calculations of the statistical significance of various effects (replicate, inhibitor regimen and level, etc.) on mortality were performed using a categorical modelling procedure (SAS PROC CATMOD). The procedure fit linear models to functions relating response frequencies to categorical data. The dependent variable Y_{ij} is defined as the logit of the proportion of animals dead,

$$Y_{ij} = \log (p_{ij}/(1-p_{ij}))$$

where p_{ij} = proportion of animals dead in response group i, replicate j.

Four categorical models were analyzed using PROC CATMOD as described in the following. In each model, the X^2 and associated probability under the null hypothesis H_0:(no effect) were calculated for the HD-dosed groups (Groups D through K).

In the first model, the data from each replicate of an experiment were analyzed separately to check for group effects. Parameter estimates were calculated for each of the HD-dosed groups. The signs of the parameter estimates for each group were compared across replicates to determine whether the treatment effect relative to Group K changed from replicate to replicate for any of the groups. If for any group the parameter estimate signs were different across replicates and if in either replicate that group was significantly ($P < 0.05$) different from Group K, then pooling of that group's data across replicates was not warranted. Otherwise (pending confirmation by the test described in the next paragraph), the mortality data were pooled across replicates.

In the second model, data were pooled between replicates in each experiment, and the X^2 and associated probabilities for the effects of group, replicate, and group-by-replicate interaction were calculated for the HD-dosed groups (Groups D through K). For any experiment in which the group-by-replicate interaction effect was significant, the mortality data were not pooled across replicates. In this categorical analysis model, the significance of the replicate effect by itself was not used as the criterion for poolability. Evidence from analysis of means tests among the Groups K across experiments revealed that the target HD dose was not consistently delivered from one replicate to the next.(1) That is, the mortality rates differed from replicate to replicate within some experiments. However, as long as the group-by-replicate interaction was not significant ($P > 0.05$), then the inconsistent administration of HD from replicate to replicate did not impair the objective of assessing treatment effect.

Subset selection procedures of Gibbons et al. were used to compare the treatment groups with control Group K.(2) The subset of treatment groups significantly better (i.e., with lower mortality rates) than the control group was determined.

A treatment group was classified as significantly better than the control (Group K) if

$$x_j < x_K - d_\alpha (S'_j)$$

where x_j is the mean response for treatment Group J, the subscript K denotes the control Group K,

d_α is the entry in Table A.1 of Gibbons et al. corresponding to the number of groups ($k = 8$) and $P^* = 1 - \alpha$, and

S'_j denotes an estimate of the standard error of the mean response.

The factor d_α is related to Dunnett's factor for comparisons between treatments and a control, and equals 3.31 for $\alpha = 0.05$ in this application.

The quantities x_j and S'_j were calculated from the results of SAS PROC CATMOD as follows. CATMOD calculated predicted logit values and standard errors for each of the 16 (8 treatments x 2 replicates) subsets of the data. To obtain a single predicted value (x_j) for the logit for each of the eight treatment groups, the predicted logit function values were averaged over the two replicates within each treatment group.

The subset selection procedure specified that the subsets (populations) being compared have a common standard error. This was satisfied only approximately for the logit responses. To calculate standard errors for comparison purposes, the following computations were made using the standard errors for the predicted function values in CATMOD.

1. Within each treatment group the standard errors corresponding to the two replicates were averaged (SE_j).

2. This average standard error (SE_j) was adjusted for the replicate component by calculating

$$ASE_j = \sqrt{SE^2_j - SE^2_R}$$

where SE_R was the standard error of the estimate of the replicate parameter in the linear model.

3. For comparing x_j with $x_{[k]}$ the S'_j was calculated as

$$S'_j = \sqrt{(ASE^2_j + ASE^2_{[k]})/2} \quad .$$

In the third model, the X^2 and associated probabilities were calculated by experiment for the four effects of inhibitor level (low or high), inhibitor regimen (1 hr before, 1 hr after, or 1 and 4 hr after), level-by-regimen interaction, and replicate. This model excluded Groups F and K, which did not fit into the 2-by-3 structuring, and revealed whether the inhibitor treatment variables generally affected the mortality rates and whether there was a significant interaction of when and how much inhibitor was given.

Finally, within each pooled experiment the X^2 and associated probabilities were calculated for the effects of the total dose of inhibitor administered (regardless of when it was administered), replicate, and the total inhibitor-by-replicate interaction. Total inhibitor was calculated as the number of doses multiplied times the dose administered per injection. All HD-dosed groups were included in this analysis. For experiments in which the analysis revealed a significant interaction term, the procedure was repeated by replicate under the null hypothesis H_0:(no effect due to amount of total inhibitor). Mortality rates were plotted versus total inhibitor for all experiments.

Hematology Data

All analyses of hematologic variables employed a general linear modelling procedure (SAS PROC GLM) to test for various effects across the logarithm of time. Time values were transformed by $\log_{10}$ to prevent undue influence by the 30-day values, and to allow results to represent effects at the average $\log_{10}$ time of 3.9 days instead of at the average time of 7.5 days. The time of 3.9 days was preferred because at that time the animals generally were exhibiting the greatest deviation in their hemograms from normal, whereas by 7.5 days the survivors were on their way to recovery. Since the objective of this part of the study was to detect the effect of the inhibitors when the immune systems of the animals were severely compromised, the $\log_{10}$ transformed time values were used.

The analysis of hematologic data for no-HD control Groups A, B, and C was performed separately from that of the HD-dosed groups. The purpose of this work was to determine the possible toxic effects of the inhibitor solutions alone, i.e., without the influence of HD. Since the no-HD groups were not replicated in any of the experiments, the results from only 2 days per inhibitor were used, namely, the first replicate at each HD dose level. In order to conserve animals, Group A controls were included only for the dosing days on which HD-dosed groups received HD at the LD_{60}. Thus for each inhibitor, all Group A data came from one replicate.

For each inhibitor, a 12-parameter ANOVA model was used to test for the effects of the intercept, inhibitor level (in mg/kg), the day of dosing, the level-by-day-of-dosing interaction, $level^2$, time after dosing, $time^2$, $time^3$, and the four linear and quadratic combinations of level and time.

The analysis of hematologic data from the HD-dosed groups involved three ANOVA models, each performed by experiment as presented below. Data were plotted for experiments in which the main (excluding replicate) effects in at least one of the models was significant ($P < 0.05$).

In the first model, the ANOVA tested for the effects of group, replicate, time after dosing, $time^2$, $time^3$, and the three interactions of group-by-time, $-time^2$, and $-time^3$. This model determined whether there were any significant ($P < 0.05$) differences among groups in the overall time course of each hematologic variable.

In the second model, the effects tested were the total amount of inhibitor administered (irrespective of when it was administered), time after dosing, the square and cube of both these, the four linear and quadratic interactions, and replicate. This model was designed to determine whether there was any association of net amount of inhibitor administered with the time course of the hemogram.

In the third model, the effects tested were replicate, inhibitor level (low or high), inhibitor regimen, the level-by-regimen interaction, time after dosing, $time^2$, and $time^3$. This model was designed to determine whether structuring the group descriptor values could lead to detection of effects not apparent in the first (unstructured) model.

REFERENCES

(1) Ott, F. R. 1975. Process Quality Control. McGraw-Hill, New York.

(2) Gibbons, J. D., Olkin, I., and Sobel, M. 1977. Selecting and Ordering Populations: A New Statistical Methodology. John Wiley, New York.

APPENDIX E

Tables

TABLE 2.1. GROUPS INCLUDED AND THE NUMBER OF ANIMALS USED* PER GROUP IN THE INHIBITOR STUDIES

	Target HD Dose											
	LD_{30}						LD_{60}					
Inhibitor:	3AB		NIC		NA		3AB		NIC		NA	
Replicate:	1	2	1	2	1	2	1	2	1	2	1	2
Group												
A	0	0	0	0	0	0	10	0	10	0	10	0
B	9	0	9	0	10	0	10	0	10	0	10	0
C	10	0	10	0	10	0	10	0	10	0	10	0
D	10	10	10	10	10	10	10	10	9	10	9	10
E	10	10	10	10	10	10	10	10	10	10	10	9
F	10	10	10	10	10	10	10	10	9	10	10	10
G	10	10	10	10	10	10	9	10	10	10	10	10
H	10	10	10	10	10	10	10	7	10	10	10	10
I	10	10	10	10	10	10	10	10	10	10	10	10
J	10	9	10	10	10	10	10	10	9	10	9	10
K	30	30	10	10	30	30	29	30	9	10	30	30

3AB = 3-Aminobenzamide
NIC = Nicotinamide
NA = Nicotinic Acid

*Animals in some groups were not correctly dosed and are not counted in the above table.

TABLE 3.1. MORTALITY PROFILE OVER 14-DAY OBSERVATION PERIOD OF MICE GIVEN SUBCUTANEOUS DOSES OF HD

Dose (mg/kg)	Number Dosed	Number of Deaths														Total Deaths
		Day														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Replicate 1 (January 31, 1985)																
0.0	10	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
15.9	10	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
18.4	10	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
21.2	10	0	0	0	0	2	2	0	0	0	0	0	0	0	0	4
28.2	10	0	2	2	0	0	1	0	0	0	0	0	0	0	0	5
32.6	10	0	0	2	0	0	1	2	0	0	0	0	0	0	0	5
37.6	10	0	1	4	2	0	1	1	0	0	0	0	0	0	0	9
50.1	10	0	2	4	1	1	0	2	0	0	0	0	0	0	0	10
Replicate 2 (February 12, 1985)																
14.7	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17.1	10	0	0	0	0	0	1	1	0	0	0	0	0	0	0	2
19.6	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26.1	10	0	0	0	1	0	3	0	0	0	0	0	0	0	0	4
30.2	10	0	0	1	0	0	2	1	0	0	0	0	0	0	0	4
34.8	10	0	0	1	0	0	2	3	1	0	0	0	0	0	0	7
46.4	10	0	0	3	2	0	2	0	0	0	0	0	0	0	0	7
Replicate 3 (February 26, 1985)																
0.0	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20.0	10	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
23.5	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27.5	10	0	0	0	0	0	1	1	0	0	0	0	0	0	0	2
32.3	10	0	0	0	0	1	2	2	2	0	0	0	0	0	0	7
37.8	10	0	0	0	0	2	3	3	0	0	0	0	0	0	0	8
44.4	10	0	0	0	0	0	4	4	2	0	0	0	0	0	0	10
52.0	10	0	0	2	1	0	4	2	1	0	0	0	0	0	0	10

TABLE 3.2. MEDIAN MORTALITY VALUES (14-DAY LD_{50}, mg/kg) FOR SUBCUTANEOUS INJECTION OF HD INTO MICE

Treatment	N	LD_{50}	LL	UL	Slope ± 1 S.E.
Replicate 1	70	26.8	23.4	30.9	6.24
Replicate 2	70	32.3	27.5	40.9	4.99
Replicate 3	70	30.6	28.0	33.5	11.4
Composite	210	29.4	27.4	31.7	6.59 ± 0.78

N = Number of mice.
LL = Lower 95% confidence limit.
UL = Upper 95% confidence limit.
S.E. = Standard error.

TABLE 3.3. MORTALITY PROFILE OVER 30-DAY OBSERVATION PERIOD OF MICE GIVEN SUBCUTANEOUS DOSES OF HD

Dose* (mg/kg)	Number Dosed	Number of Deaths, Day 1	2	3	4	5	6	7	8	9	10 to 30	Total Deaths
Replicate 1 (April 9, 1985)												
0.0	10	0	0	0	0	0	0	0	0	0	0	0
22.7	10	0	0	0	0	0	1	1	1	0	0	3
26.1	10	0	0	2	0	0	1	1	0	0	0	4
30.1	10	0	1	0	1	0	3	1	0	0	0	6
30.2	10	0	1	3	2	0	3	0	0	0	0	9
32.4	10	0	1	2	1	0	0	2	0	1	0	7
38.9	10	0	1	3	0	0	4	2	0	0	0	10
46.8	10	0	1	1	3	0	3	1	0	0	0	9
Replicate 2 (May 13, 1985)												
0.0	10	0	0	0	0	0	0	0	0	0	0	0
18.5	10	0	0	0	1	0	1	0	0	0	0	2
20.6	10	0	0	0	0	0	2	0	0	0	0	2
23.3	10	0	0	1	0	0	0	0	1	0	0	2
24.6	10	0	0	0	1	1	1	1	0	0	0	4
27.1	10	0	0	1	1	0	1	3	0	0	0	6
30.4	10	0	0	0	0	2	1	1	1	1	0	6
31.7	10	0	0	0	0	0	3	4	0	0	0	7

*As determined by gas chromatography.

TABLE 3.4. MEDIAN LETHALITY VALUES (30-DAY LD_{50}, mg/kg) FOR SUBCUTANEOUS INJECTION OF HD INTO MICE

Treatment	N	LD_{50}	LL	UL	Slope ± 1 S.E.
Replicate 1	70	26.2	21.3	29.1	7.53
Replicate 2	70	27.0	24.1	33.0	6.58
Composite	140	26.5	24.4	28.5	7.30 ± 1.33

N = Number of mice.
LL = Lower 95% confidence limit.
UL = Upper 95% confidence limit.
S.E. = Standard error.

TABLE 3.5. 7-DAY AND 14-DAY COMPOSITE MORTALITY FRACTIONS FROM 14-DAY AND 30-DAY LETHALITY STUDIES AFTER SUBCUTANEOUS INJECTION OF HD INTO MICE

Study	Dose (mg/kg)	Number Dosed	Total Number Dead After 7 Days	Total Number Dead After 14 Days
Replicate 1 (January 31, 1985)				
	0.0	10	1	1
	15.9	10	1	1
	18.4	10	1	1
	21.2	10	4	4
	28.2	10	5	5
	32.6	10	5	5
	37.6	10	9	9
	50.1	10	10	10
Replicate 2 (February 12, 1985)				
	14.7	10	0	0
	17.1	10	2	2
	19.6	10	0	0
	26.1	10	4	4
	30.2	10	4	4
	34.8	10	6	7
	46.4	10	7	7
Replicate 3 (February 26, 1985)				
	0.0	10	0	0
	20.0	10	0	1
	23.5	10	0	0
	27.5	10	2	2
	32.3	10	5	7
	37.8	10	8	8
	44.4	10	8	10
	52.0	10	9	10

TABLE 3.5.
(Continued)

Study	Dose (mg/kg)	Number Dosed	Total Number Dead After 7 Days	14 Days
Replicate 1 (April 9, 1985)				
	0.0	10	0	0
	22.7	10	2	3
	26.1	10	4	4
	30.1	10	6	6
	30.2	10	9	9
	32.4	10	6	7
	38.9	10	10	10
	46.8	10	9	9
Replicate 2 (May 13, 1985)				
	0.0	10	0	0
	18.5	10	2	2
	20.6	10	2	2
	23.3	10	1	2
	24.6	10	4	4
	27.1	10	6	6
	30.4	10	4	6
	31.7	10	7	7

TABLE 3.6. MEDIAN LETHALITY VALUES (7-DAY AND 14-DAY COMPOSITE LD_{50}, mg/kg) FROM 14-DAY AND 30-DAY DOSE-RESPONSE STUDIES AFTER SUBCUTANEOUS INJECTION OF HD INTO MICE

Treatment	N	LD_{50}	LL	UL	Slope ± 1 S.E.
Composite 7-Day	350	29.3	27.7	31.1	6.13 ± 0.63
Composite 14-Day	350	28.0	26.6	29.6	6.68 ± 0.66

N = Number of mice.
LL = Lower 95% confidence limit.
UL = Upper 95% confidence limit.
S.E. = Standard error.

TABLE 3.7. RESULTS OF F TESTS TO CONFIRM REPLICATE POOLABILITY AND TO DETERMINE AN 11-PARAMETER MULTIPLE REGRESSION MODEL GOODNESS OF FIT TO DATA

	Hematology Variable				
	WBC	ABSLYMPH	ABSSEG	MICNORM	MICPOLY
Poolability Test					
Σdf	117	117	117	120	62
Critical $F'(11,\Sigma df)$	2.10	2.10	2.10	2.10	2.21
$F(11,\Sigma df)$	3.30*	2.23*	2.81*	2.80*	1.27
11-Parameter Goodness of Fit to Data					
df_{least}	62	62	62	65	32
Critical $F'(66,\text{least})$	1.64	1.64	1.64	1.61	1.93
$F(66,\text{least})$	1.25	1.48	0.94	1.37	1.72

WBC = White Blood Cells (thousands per $\mu\ell$)
ABSSEG = Absolute Segmented Neutrophils (thousands per $\mu\ell$)
ABSLYMPH = Absolute Lymphocytes (thousands per $\mu\ell$)
MICNORM = Micronucleated Cells/500 Normochromatic Erythrocytes
MICPOLY = Micronucleated Cells/500 Polychromatic Erythrocytes

*Variance for this hematology variable was significantly ($P < 0.05$, 2-sided) greater between replicates than within replicates. However, the definitive test for replicate poolability, the chi-square test on mortality rates, showed that the replicates could be pooled.

TABLE 3.8. INDIVIDUAL ANIMAL HEMATOLOGY DATA FOR THE DOSES IN TWO REPLICATES OF THE 30-DAY LD_{50} LETHALITY STUDIES AFTER SUBCUTANEOUS INJECTION OF HD INTO MICE

DAY	ANIMAL	WBC	BAND	SEG	LYMPH	MONO	EOS	BASO	NRBC	MICNORM	MICPOLY
					Dose = 0 mg/kg						
1	M287M	5.2	0	12	87	0	1	0	0	0	1
1	M324M	3.6	0	28	71	0	1	0	0	1	0
1	M716M	5.4	0	11	89	0	0	0	0	1	1
1	M755M	*	*	*	*	*	*	*	*	*	*
2	M281M	6.6	0	25	75	0	0	0	0	1	2
2	M359M	QNS	0	15	85	0	0	0	0	0	1
2	M695M	9.6	0	15	85	0	0	0	0	1	0
2	M719M	10.0	1	40	57	1	1	0	0	0	2
3	M323M	4.4	0	33	67	0	0	0	0	1	1
3	M357M	5.8	0	19	80	0	1	0	0	1	0
3	M663M	5.4	0	5	94	0	1	0	0	1	2
3	M667M	7.8	0	5	94	0	1	0	0	1	2
4	M276M	6.2	0	7	93	0	0	0	0	0	0
4	M325M	5.8	0	14	83	0	3	0	0	0	2
4	M696M	6.8	0	12	88	0	0	0	0	1	2
4	M712M	4.4	0	18	78	0	4	0	0	1	2
5	M311M	5.6	0	22	78	0	0	0	0	0	2
5	M312M	5.6	0	15	83	0	2	0	0	1	2
5	M731M	7.8	1	29	70	0	0	0	0	1	1
5	M755M	8.0	0	9	91	0	0	0	0	1	2
					Dose = 18.5 mg/kg						
1	M743M	2.0	0	47	53	0	0	0	0	1	2
1	M763M	*	*	*	*	*	*	*	*	*	*
2	M694M	2.6	0	66	34	0	0	0	0	2	#
2	M707M	4.8	0	87	12	0	1	0	0	1	2
3	M671M	0.2	0	18	82	0	0	0	1	1	#
3	M730M	1.2	0	5	95	0	0	0	0	1	#
4	M672M	1.2	0	0	100	0	0	0	0	1	4
4	M752M	1.4	0	2	98	0	0	0	0	1	#
5	M743M	1.4	0	10	90	0	0	0	0	1	1
5	M763M	0.8	0	4	96	0	0	0	0	1	1

Note: See page E-15 for an explanation of blood parameters and symbols used.

TABLE 3.8.
(Continued)

DAY	ANIMAL	WBC	BAND	SEG	LYMPH	MONO	EOS	BASO	NRBC	MICNORM	MICPOLY
					Dose = 20.6 mg/kg						
1	M732M	*	*	*	*	*	*	*	*	*	*
1	M734M	3.8	0	85	14	0	1	0	0	1	1
2	M651M	3.6	0	39	61	0	0	0	0	1	#
2	M701M	10.0	0	24	76	0	0	0	0	2	8
3	M721M	2.2	0	29	71	0	0	0	0	1	#
3	M750M	0.6	0	66	34	0	0	0	0	1	5
4	M665M	15.6°	0	44	54	0	2	0	0	1	1
4	M681M	1.0	0	12	88	0	0	0	0	2	0
5	M732M	2.4	0	11	88	0	1	0	0	2	2
5	M756M	1.0	0	6	94	0	0	0	0	1	#
					Dose = 22.7 mg/kg						
1	M260M	1.4	0	72	28	0	0	0	0	1	0
1	M329M	3.4	3	86	11	0	0	0	0	1	3
2	M285M	2.4	0	78	22	0	0	0	0	1	6
2	M286M	2.0	0	55	45	0	0	0	0	2	4
3	M265M	0.8	0	14	86	0	0	0	0	0	0
3	M362M	3.8	0	16	84	0	0	0	0	1	3
4	M256M	1.0	0	4	96	0	0	0	0	0	#
4	M339M	0.8	1	4	95	0	0	0	0	1	#
5	M289M	0.4	0	3	97	0	0	0	0	0	#
5	M305M	0.2	0	5	95	0	0	0	0	1	#
					Dose = 23.3 mg/kg						
1	M658M	1.2	1	74	25	0	0	0	0	1	4
1	M661M	7.4	0	75	25	0	0	0	0	2	3
2	M682M	3.2	0	59	39	0	2	0	0	2	15
2	M718M	1.6	1	36	63	0	0	0	0	1	60
3	M678M	1.4	0	33	67	0	0	0	0	2	#
3	M748M	2.0	0	35	65	0	0	0	0	2	#
4	M739M	1.8	1	6	93	0	0	0	0	1	#
4	M762M	1.2	0	1	99	0	0	0	0	2	#
5	M661M	1.2	2	8	90	0	0	0	0	2	1
5	M664M	0.6	0	4	96	0	0	0	0	1	2

TABLE 3.8.
(Continued)

DAY	ANIMAL	WBC	BAND	SEG	LYMPH	MONO	EOS	BASO	NRBC	MICNORM	MICPOLY
					Dose = 24.6 mg/kg						
1	M673M	*	*	*	*	*	*	*	*	*	*
1	M692M	4.8	3	82	15	0	0	0	0	1	2
2	M656M	0.8	0	53	47	0	0	0	0	2	49
2	M708M	2.2	0	77	23	0	0	0	0	1	12
3	M688M	1.6	0	25	75	0	0	0	0	1	#
3	M691M	2.6	0	31	69	0	0	0	0	1	#
4	M723M	0.6	0	5	95	0	0	0	0	2	#
4	M761M	0.0	0	0	0	0	0	0	0	1	#
5	M688M	1.2	0	1	99	0	0	0	0	1	2
5	M691M	3.4	0	1	99	0	0	0	0	1	3
					Dose = 26.1 mg/kg						
1	M332M	1.4	0	54	46	0	0	0	0	0	7
1	M336M	2.0	0	51	48	0	1	0	0	1	0
2	M302M	2.8	0	42	58	0	0	0	0	1	#
2	M310M	1.2	0	23	75	0	2	0	0	1	#
3	M278M	1.2	0	18	82	0	0	0	0	2	#
3	M347M	0.8	0	8	92	0	0	0	0	1	#
4	M271M	0.4	0	6	94	0	0	0	0	0	#
4	M295M	0.6	0	1	99	0	0	0	0	0	#
5	M332M	0.4	0	1	99	0	0	0	0	0	#
5	M336M	0.8	0	2	98	0	0	0	0	0	0
					Dose = 27.1 mg/kg						
1	M745M	6.2	0	89	11	0	0	0	0	1	1
1	M751M	4.4	0	68	31	0	1	0	0	1	2
2	M659M	4.6	0	95	5	0	0	0	0	3	1
2	M705M	1.6	0	58	42	0	0	0	0	2	#
3	M757M	1.6	0	94	6	0	0	0	0	1	#
3	M758M	2.8	0	50	50	0	0	0	0	3	#
4	M744M	2.8	0	9	91	0	0	0	0	1	8
4	M749M	2.2	0	8	91	0	1	0	0	2	2
5	M744M	3.2	0	8	92	0	0	0	0	1	4
5	M751M	1.6	0	15	85	0	0	0	0	2	3

TABLE 3.8.
(Continued)

DAY	ANIMAL	WBC	BAND	SEG	LYMPH	MONO	EOS	BASO	NRBC	MICNORM	MICPOLY
					Dose = 30.1 mg/kg						
1	M251M	1.6	0	71	29	0	0	0	0	1	4
1	M298M	2.4	0	92	7	0	1	0	0	2	6
2	M330M	3.6	0	52	49	0	1	0	0	2	24
2	M346M	0.8	0	87	12	0	1	0	0	1	5
3	M258M	0.4	0	13	87	0	0	0	0	2	#
3	M294M	3.0	0	44	56	0	0	0	0	3	#
4	M280M	0.2	0	4	96	0	0	0	0	1	#
4	M315M	0.8	0	2	98	0	0	0	0	1	#
5	M294M	0.6	1	1	98	0	0	0	0	0	#
5	M330M	1.0	0	0	100	0	0	0	0	1	1
					Dose 30.2 mg/kg						
1	M270M	3.6	0	94	6	0	0	0	0	2	3
1	M320M	QNS	QNS	QNS	QNS	QNS	QNS	QNS	QNS	QNS	QNS
2	M314M	4.8	0	84	15	0	1	0	0	1	2
2	M322M	1.0	0	84	15	0	1	0	0	2	14
3	M270M	0.4	0	13	87	0	0	0	0	1	*
3	M363M	0.8	0	47	52	0	1	0	0	2	*
4	M314M	*	*	*	*	*	*	*	*	*	*
4	M322M	0.2	0	9	91	0	0	0	0	1	*
5	M314M	*	*	*	*	*	*	*	*	*	*
					Dose = 30.4 mg/kg						
1	M709M	3.4	1	74	25	0	0	0	0	1	1
1	M740M	6.2	0	90	10	0	0	0	0	1	1
2	M693M	3.4	0	80	19	0	1	0	0	1	2
2	M759M	4.0	0	94	5	0	1	0	0	1	#
3	M729M	12.0°	0	38	62	0	0	0	0	1	2
3	M741M	1.0	0	7	93	0	0	0	0	2	#
4	M709M	0.8	0	5	95	0	0	0	0	1	#
4	M740M	0.6	0	7	93	0	0	0	0	2	0
5	M693M	2.6	0	4	96	0	0	0	0	1	#
5	M729M	20.0°	1	70	29	0	0	0	0	1	1

TABLE 3.8.
(Continued)

DAY	ANIMAL	WBC	BAND	SEG	LYMPH	MONO	EOS	BASO	NRBC	MICNORM	MICPOLY
					Dose = 31.7 mg/kg						
1	M689M	2.4	0	82	18	0	0	0	0	1	1
1	M713M	5.0	0	94	6	0	C	0	0	1	1
2	M655M	3.6	0	53	47	0	0	0	0	1	52
2	M668M	2.6	0	52	48	0	0	0	0	1	#
3	M703M	0.2	0	24	76	0	0	0	0	1	#
3	M735M	0.4	0	35	65	0	0	0	0	1	#
4	M685M	0.8	0	10	90	0	0	0	0	1	#
4	M764M	0.4	0	11	89	0	0	0	0	1	#
5	M724M	0.2	0	1	99	0	0	0	0	1	#
5	M735M	QNS	QNS	QNS	QNS	QNS	QNS	QNS	QNS	1	#
					Dose = 32.4 mg/kg						
1	M274M	1.8	1	89	10	0	0	0	0	2	5
1	M279M	1.8	0	42	58	0	0	0	1	1	13
2	M299M	2.8	0	95	5	0	0	0	0	2	7
2	M307M	1.2	0	87	13	0	0	0	0	1	2
3	M318M	1.8	0	7	93	0	0	0	0	1	#
3	M331M	0.6	0	6	94	0	0	0	0	2	#
4	M274M	0.2	0	3	97	0	0	0	0	1	#
4	M279M	*	*	*	*	*	*	*	*	*	*
5	M274M	0.2	0	7	93	0	0	0	0	0	5
5	M299M	0.1	0	0	100	0	0	0	0	1	#
					Dose = 38.9 mg/kg						
1	M306M	2.2	0	90	10	0	0	0	0	1	1
1	M319M	1.2	0	61	37	0	2	0	0	1	1
2	M273M	1.8	0	66	33	0	1	0	0	1	6
2	M326M	2.8	0	67	33	0	0	0	0	1	6
3	M304M	1.6	2	4	94	0	0	0	0	1	*
3	M316M	0.6	0	68	32	0	0	0	0	1	*
4	M319M	0.2	0	2	98	0	0	0	1	0	*
4	M326M	*	*	*	*	*	*	*	*	*	*
5	M319M	QNS	QNS	QNS	QNS	QNS	QNS	QNS	QNS	QNS	QNS

TABLE 3.8.
(Continued)

DAY	ANIMAL	WBC	BAND	SEG	LYMPH	MONO	EOS	BASO	NRBC	MICNORM	MICPOLY
					Dose = 46.8 mg/kg						
1	M335M	1.2	0	63	37	0	0	0	0	2	3
1	M350M	2.4	0	82	18	0	0	0	0	1	5
2	M268M	0.2	0	22	78	0	0	0	0	2	#
2	M288M	2.2	0	92	8	0	0	0	0	1	9
3	M284M	1.0	0	69	31	0	0	0	0	2	5
3	M296M	1.2	0	26	74	0	0	0	0	1	#
4	M284M	*	*	*	*	*	*	*	*	*	*
4	M350M	*	*	*	*	*	*	*	*	*	*
5	M296M	0.6	0	5	95	0	0	0	0	1	#

WBC = White Blood Cells (thousands per $\mu\ell$)
BAND = Non-segmented Neutrophils (percent of total WBC)
SEG = Segmented Neutrophils (percent of total WBC)
LYMPH = Lymphocytes (percent of total WBC)
MONO = Monocytes (percent of total WBC)
EOS = Eosinophils (percent of total WBC)
BASO = Basophils (percent of total WBC)
NRBC = Nucleated Red Blood Cells (number per 100 WBC)
MICNORM = Micronucleated Cells/500 Normochromatic Erythrocytes
MICPOLY = Micronucleated Cells/500 Polychromatic Erythrocytes
* = Clotted blood sample
QNS = Quantity not sufficient
# = Polychromatic cells too few for quantitation of micronuclei
° = Outlier at α = 0.05, 2-sided

TABLE 3.9. MREF PROTOCOL 18 HEMATOLOGY DATA 30-DAY LD_{50} REPLICATES 1 AND 2 GROUPS* MERGED BETWEEN REPLICATES BY DOSE LEVELS

		WBC			ABSSEG			ABSLYMPH		
		N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
SET	DAY									
1	1	3	4.73	0.99	3	0.74	0.23	3	3.96	1.23
	2	3	8.73	1.86	3	2.36	1.42	3	6.27	1.68
	3	4	5.85	1.43	4	0.80	0.57	4	5.00	1.81
	4	4	5.80	1.02	4	0.71	0.19	4	5.00	1.16
	5	4	6.75	1.33	4	1.26	0.70	4	5.44	1.31
2	1	2	2.90	1.27	2	2.09	1.62	2	0.80	0.37
	2	4	5.25	3.29	4	2.42	1.24	4	2.81	3.27
	3	4	1.05	0.87	4	0.28	0.29	4	0.77	0.70
	4	3	1.20	0.20	3	0.05	0.06	3	1.15	0.25
	5	4	1.40	0.71	4	0.12	0.10	4	1.27	0.60
3	1	5	3.64	2.57	5	2.86	1.98	5	0.73	0.65
	2	6	2.03	0.80	6	1.26	0.66	6	0.76	0.34
	3	6	2.03	1.05	6	0.51	0.25	6	1.52	0.90
	4	5	1.08	0.46	5	0.04	0.04	5	1.03	0.43
	5	6	1.17	1.17	6	0.03	0.03	6	1.13	1.16
4	1	4	3.5	2.22	4	2.57	2.20	4	0.91	0.33
	2	4	2.55	1.53	4	1.69	1.83	4	0.86	0.58

Note: See page E-20 for an explanation of blood parameters and symbols used.

TABLE 3.9.
(Continued)

SET	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
	3	4	1.60	0.86	4	0.80	0.76	4	0.80	0.55
	4	4	1.50	1.18	4	0.11	0.12	4	1.38	1.06
	5	4	1.50	1.24	4	0.13	0.14	4	1.37	1.12
5	1	9	3.13	1.59	9	2.65	1.62	9	0.47	0.31
	2	10	2.78	1.37	10	2.09	1.18	10	0.68	0.66
	3	9	0.96	0.90	9	0.25	0.42	9	0.71	0.59
	4	8	0.50	0.28	8	0.03	0.02	8	0.47	0.27
	5	6	0.78	0.95	6	0.02	0.04	6	0.76	0.91
6	1	2	1.70	0.71	2	1.36	0.88	2	0.33	0.16
	2	2	2.30	0.71	2	1.53	0.49	2	0.76	0.23
	3	2	1.10	0.71	2	0.24	0.24	2	0.85	0.93
	4	1	0.20	.	1	0.00	.	1	0.20	.
	5	0	.	.	0	.	.	0	.	.
7	1	2	1.80	0.85	2	1.36	0.86	2	0.44	0.01
	2	2	1.20	1.41	2	1.03	1.40	2	0.17	0.01
	3	2	1.10	0.14	2	0.50	0.27	2	0.60	0.41
	4	0	.	.	0	.	.	0	.	.
	5	1	0.60	.	1	0.03	.	1	0.57	.

TABLE 3.9.
(Continued)

		MICNORM			MICPOLY		
		N	MEAN	STD	N	MEAN	STD
SET	DAY						
1	1	3	0.67	0.58	3	0.67	0.58
	2	4	0.50	0.58	4	1.25	0.96
	3	4	1.00	0.00	4	1.25	0.96
	4	4	0.50	0.58	4	1.50	1.00
	5	4	0.75	0.50	4	1.75	0.50
2	1	2	1.00	0.00	2	1.50	0.71
	2	4	1.50	0.58	2	5.00	4.24
	3	4	1.00	0.00	1	5.00	.
	4	3	1.33	0.58	2	2.00	2.83
	5	4	1.25	0.50	3	1.33	0.58
3	1	5	1.20	0.45	5	2.40	1.52
	2	6	1.50	0.55	6	24.33	23.96
	3	6	1.17	0.75	2	1.50	2.12
	4	6	1.17	0.75	0	.	.
	5	6	1.00	0.63	4	2.00	0.82
4	1	4	0.75	0.50	4	2.50	3.11
	2	4	1.75	0.96	1	1.00	.
	3	4	1.75	0.96	0	.	.

TABLE 3.9.
(Continued)

SET	DAY	MICNORM N	MICNORM MEAN	MICNORM STD	MICPOLY N	MICPOLY MEAN	MICPOLY STD
	4	4	0.75	0.96	2	5.00	4.24
	5	4	0.75	0.96	3	2.33	2.08
5	1	9	1.33	0.50	9	3.89	3.92
	2	10	1.20	0.63	8	13.50	17.34
	3	9	1.67	0.71	0	.	.
	4	8	1.13	0.35	1	0.00	.
	5	7	0.71	0.49	2	3.00	2.83
6	1	2	1.00	0.00	2	1.00	0.00
	2	2	1.00	0.00	2	6.00	0.00
	3	2	1.00	0.00	0	.	.
	4	1	0.00	.	0	.	.
	5	0	.	.	0	.	.
7	1	2	1.50	0.71	2	4.00	1.41
	2	2	1.50	0.71	1	9.00	.
	3	2	1.50	0.71	1	5.00	.
	4	0	.	.	0	.	.
	5	1	1.00	.	0	.	.

TABLE 3.9.
(Continued)

*	= As represented in Figures 3.5 through 3.9.
.	= Could not be calculated either because all data were missing or (in cases of standard deviations) because the sample size was 1.
WBC	= White Blood Cells (thousands per $\mu\ell$)
ABSSEG	= Absolute Segmented Neutrophils (thousands per $\mu\ell$)
ABSLYMPH	= Absolute Lymphocytes (thousands per $\mu\ell$)
MICNORM	= Micronucleated Cells/500 Normochromatic Erythrocytes
MICPOLY	= Micronucleated Cells/500 Polychromatic Erythrocytes
N	= Number of animals used
STD	= Standard deviation

TABLE 3.10. STATISTICALLY SIGNIFICANT ($P < 0.05$) EFFECTS IN AN 11-PARAMETER REGRESSION MODEL FOR FIVE HEMATOLOGIC VARIABLES MEASURED FOR THE HD DOSE-RESPONSE STUDIES

Parameter	Hematology Variable				
	WBC	ABSLYMPH	ABSSEG	MICNORM	MICPOLY
Intercept	***	***	***	***	***
Day	*	.	***	.	*
Day^2	.	.	***	*	*
Day^3	.	.	**	.	*
Dose	.	**	.	.	.
$Dose^2$	.	***	.	.	.
$Dose^3$	.	.	.	.	.
Day-by-Dose	.	.	.	.	.
Day-by-$Dose^2$	.	.	**	.	.
Day^2-by-Dose	.	.	.	.	.
Day^2-by-$Dose^2$	.	.	.	.	.

. = $P > 0.05$
* = $0.05 > P > 0.01$
** = $0.01 > P > 0.001$
*** = $P < 0.001$
WBC = White Blood Cells (thousands per $\mu\ell$)
ABSSEG = Absolute Segmented Neutrophils (thousands per $\mu\ell$)
ABSLYMPH = Absolute Lymphocytes (thousands per $\mu\ell$)
MICNORM = Micronucleated Cells/500 Normochromatic Erythrocytes
MICPOLY = Micronucleated Cells/500 Polychromatic Erythrocytes

TABLE 3.11. CORRELATION COEFFICIENTS FOR HEMATOLOGIC VARIABLES VERSUS PERCENT MORTALITY FOR ALL GROUPS COMBINED ACROSS REPLICATES BY PROXIMAL DOSE LEVELS

HD Dose Range (mg/kg)	Hematology Variable				
	WBC	ABSLYMPH	ABSSEG	MICNORM	MICPOLY
0 - 21	-0.286	-0.098	-0.392	-0.308	-0.172
22 - 25	-0.137	0.376*	-0.376*	0.231	-0.240
26 - 28	-0.509*	0.255	-0.636*	-0.192	0.227
29 - 33	-0.435*	-0.075	-0.431*	-0.115	-0.059
34 - 40	-0.637	0.168	-0.806*	-0.461	1.000*
41 - 47	-0.490	0.346	-0.567	-0.311	0.346

* = Significant ($P < 0.05$) correlation
WBC = White Blood Cells (thousands per $\mu\ell$)
ABSSEG = Absolute Segmented Neutrophils (thousands per $\mu\ell$)
ABSLYMPH = Absolute Lymphocytes (thousands per $\mu\ell$)
MICNORM = Micronucleated Cells/500 Normochromatic Erythrocytes
MICPOLY = Micronucleated Cells/500 Polychromatic Erythrocytes

TABLE 3.12. MORTALITY PROFILE OVER 30-DAY OBSERVATION PERIOD OF MICE GIVEN EITHER THE LD_{30} OR LD_{60} OF HD WITH OR WITHOUT ONE OF THREE TEST INHIBITORS OF HD TOXICITY

Target HD Dose = 22.0 mg/kg (LD_{30})
Test Inhibitor = 3-Aminobenzamide

Group	Number Dosed	Number of Deaths, Day 1	2	3	4	5	6	7	8	9	10	11	12	13	Total Deaths
Replicate 1 (March 18, 1986)															
B	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	10	0	0	0	0	0	1	0	0	0	0	0	0	0	1
E	10	0	0	0	0	2	2	0	0	0	0	0	0	0	4
F	10	0	0	0	1	5	1	0	0	0	0	0	0	0	7
G	10	0	0	0	0	1	6	0	1	0	0	0	0	0	8
H	10	0	0	0	0	0	6	0	1	0	0	0	0	0	7
I	10	0	0	0	0	0	4	0	1	0	0	0	0	0	5
J	10	0	0	0	1	0	1	3	1	0	0	0	0	1	7
K	30	0	0	0	0	1	10	2	0	0	0	0	0	1	14
Replicate 2 (April 7, 1986)															
D	10	0	0	0	0	0	2	0	0	0	0	0	0	0	2
E	10	0	0	0	0	2	0	0	0	0	0	0	0	0	2
F	10	0	0	0	0	0	2	0	1	0	0	0	0	0	3
G	10	0	0	1	1	2	3	0	0	0	0	0	0	0	7
H	10	0	0	0	0	0	4	0	0	0	0	0	0	0	4
I	10	0	0	0	0	0	2	0	0	0	0	0	0	0	2
J	9	0	0	0	0	0	0	1	0	0	0	1	0	0	2
K	30	0	0	0	0	4	4	0	1	0	0	0	0	0	9

Table 3.12
(Continued)

Target HD Dose = 22.0 mg/kg (LD_{30})
Test Inhibitor = Nicotinic Acid

Group	Number Dosed	Number of Deaths, Day 1	2	3	4	5	6	7	8	9	10	11	12	13	Total Deaths
Replicate 1 (November 19, 1985)															
B	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	10	0	0	0	0	0	4	0	0	0	0	0	0	0	4
E	10	0	0	0	0	0	3	1	0	0	0	0	0	0	4
F	10	0	0	0	0	0	3	1	0	0	0	0	0	0	4
G	10	0	0	0	0	0	5	0	0	0	0	0	0	0	5
H	10	0	0	0	0	0	2	1	1	0	0	0	0	0	4
I	9	0	0	0	0	0	2	2	0	0	0	0	0	0	4
J	9	0	0	0	0	0	2	2	0	0	0	0	0	0	4
K	29	0	0	0	0	0	12	1	0	0	0	0	0	0	13
Replicate 2 (January 6, 1986)															
D	10	0	0	0	0	0	0	1	0	0	0	0	0	0	1
E	10	0	0	0	0	1	1	1	0	0	0	0	0	0	3
F	10	0	0	0	0	0	2	0	1	0	0	0	0	0	3
G	10	0	0	0	0	1	2	0	1	0	0	0	0	0	4
H	10	0	0	0	0	0	1	0	0	0	0	0	0	0	1
I	10	0	0	0	0	1	1	1	0	1	0	0	0	0	4
J	10	0	0	0	0	1	1	0	0	0	0	0	0	0	2
K	30	0	0	0	0	2	2	5	1	0	0	0	0	0	10

Table 3.12
(Continued)

Target HD Dose = 22.0 mg/kg (LD_{30})
Test Inhibitor = Nicotinamide

Group	Number Dosed	Number of Deaths — Day 1	2	3	4	5	6	7	8	9	10	11	12	13	Total Deaths
Replicate 1 (August 20, 1985)															
B	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	10	0	0	2	0	0	1	2	1	0	0	0	0	1	7
E	10	0	0	0	1	0	0	4	1	0	0	0	0	0	6
F	10	0	0	0	0	0	1	3	0	0	0	0	0	0	4
G	10	0	0	0	0	1	1	1	0	0	0	0	0	0	3
H	10	0	0	0	0	0	0	1	2	0	0	0	0	1	4
I	10	0	0	0	0	0	2	1	3	2	0	0	0	0	8
J	10	0	0	0	0	1	1	0	0	2	0	0	0	0	4
K	10	0	0	2	0	0	3	1	1	0	0	0	0	0	7
Replicate 2 (September 9, 1985)															
D	10	0	0	0	0	0	0	1	0	0	0	0	0	1	2
E	10	0	0	0	0	0	1	0	0	0	0	0	0	0	1
F	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
G	10	0	0	0	0	0	1	1	1	0	0	0	0	0	3
H	10	0	0	0	0	0	0	1	0	0	0	0	0	0	1
I	10	0	0	0	0	0	0	0	1	0	0	0	0	0	1
J	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	10	0	0	0	0	0	1	1	0	1	0	0	0	0	3

Table 3.12
(Continued)

Target HD Dose = 28.2 mg/kg (LD_{60})
Test Inhibitor = 3-Aminobenzamide

Group	Number Dosed	Number of Deaths Day 1	2	3	4	5	6	7	8	9	10	11	12	13	Total Deaths
Replicate 1 (January 27, 1986)															
A	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	10	0	0	0	0	2	2	1	0	0	0	0	0	0	5
E	10	0	0	0	0	1	2	0	0	0	0	0	0	0	3
F	10	0	0	0	1	3	2	0	1	0	0	0	0	0	7
G	9	0	0	0	0	2	5	1	0	0	0	0	0	0	8
H	10	0	0	0	0	1	3	3	0	0	0	0	0	0	7
I	10	0	0	0	0	1	3	2	0	0	0	0	0	0	6
J	10	0	0	0	2	1	3	0	0	1	0	0	0	0	7
K	29	0	0	1	1	5	13	2	1	1	0	0	0	0	24
Replicate 2 (February 24, 1986)															
D	10	0	0	0	0	2	2	1	0	0	0	0	0	0	5
E	10	0	0	0	0	4	2	0	0	0	0	0	0	0	6
F	10	0	0	0	0	4	3	1	0	0	0	0	0	1	9
G	10	0	0	0	0	6	2	0	0	0	0	0	0	0	8
H	7	0	0	0	0	1	2	1	0	0	0	0	0	0	4
I	10	0	0	0	0	4	3	0	0	0	0	0	0	0	7
J	10	0	0	0	0	2	4	2	0	0	0	0	0	0	8
K	30	0	0	0	0	8	7	2	2	1	0	0	0	0	20

Table 3.12
(Continued)

Target HD Dose = 28.2 mg/kg (LD_{60})
Test Inhibitor = Nicotinic Acid

Group	Number Dosed	Number of Deaths — Day 1	2	3	4	5	6	7	8	9	10	11	12	13	Total Deaths
Replicate 1 (October 14, 1985)															
A	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	10	0	0	0	1	0	0	1	0	0	0	0	0	0	2
E	10	0	0	0	0	0	1	2	0	0	0	0	0	0	3
F	10	0	0	0	0	0	0	0	1	0	0	0	0	0	1
G	10	0	0	0	1	3	1	1	0	0	0	0	0	0	6
H	10	0	0	0	0	1	3	1	0	0	0	0	0	0	5
I	10	0	0	0	0	0	1	0	0	0	0	0	0	0	1
J	9	0	0	0	0	0	2	0	0	0	0	0	0	0	2
K	30	0	0	0	0	2	2	6	0	0	0	0	0	0	10
Replicate 2 (November 11, 1985)															
D	10	0	0	0	0	1	2	2	1	0	0	0	0	0	6
E	9	0	0	0	1	1	3	1	0	0	0	0	0	0	6
F	10	0	0	0	1	1	2	2	0	0	0	0	0	0	6
G	10	0	0	0	0	2	2	1	0	1	0	0	0	1	7
H	10	0	0	0	0	2	2	3	0	0	0	0	0	0	7
I	10	0	0	0	1	2	3	0	0	1	0	0	0	0	7
J	10	0	0	0	0	0	4	1	0	1	0	0	0	0	6
K	30	0	0	1	2	3	11	4	3	0	0	0	0	0	24

Table 3.12
(Continued)

Target HD Dose = 28.2 mg/kg (LD_{60})
Test Inhibitor = Nicotinamide

Group	Number Dosed	Number of Deaths – Day 1	2	3	4	5	6	7	8	9	10	11	12	13	Total Deaths
Replicate 1 (July 8, 1985)															
A	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	9	0	1	0	1	0	1	2	1	0	0	0	0	0	6
E	10	0	0	0	0	0	3	4	1	0	0	0	0	0	8
F	9	0	0	0	0	2	4	2	0	0	0	0	0	0	8
G	10	0	0	1	1	0	4	1	2	0	0	0	1	0	10
H	10	0	0	0	0	1	4	2	0	0	0	0	0	0	7
I	10	0	0	0	0	0	0	6	1	0	0	0	0	0	7
J	9	0	0	0	0	0	2	3	0	0	0	0	0	0	5
K	9	0	0	0	0	0	1	5	1	0	0	0	0	0	7
Replicate 2 (July 29, 1985)															
D	10	0	0	0	0	0	0	3	0	1	0	0	0	0	4
E	10	0	0	0	1	1	3	0	0	0	0	0	0	0	5
F	10	0	0	0	1	1	4	1	1	0	0	0	0	0	8
G	10	0	0	0	1	1	2	4	0	0	0	0	0	0	8
H	10	0	0	0	0	1	2	2	0	0	0	0	0	0	5
I	10	0	0	0	0	0	2	2	0	0	0	0	0	0	4
J	10	0	0	0	0	0	3	2	0	0	1	0	0	0	6
K	10	0	0	2	1	1	2	2	0	0	0	0	0	0	8

TABLE 3.13. CATEGORICAL MODELLING OF MORTALITY AMONG HD-DOSED GROUPS TO DETECT GROUP EFFECTS, BY EXPERIMENT

	Target HD Dose					
	LD_{30}			LD_{60}		
Inhibitor:	3AB	NIC	NA	3AB	NIC	NA
	Main Effects					
Effect						
Group	*	.	.	.	.	.
Replicate	**	***	*	.	*	***
Group-by-Replicate	.	.	.	.	.	.
	Direct Contrasts With Group K					
Group						
D	.	.	.	.	.	.
E	.	.	.	+	.	.
F	.	.	.	.	.	.
G	.	.	.	.	.	.
H	.	.	.	.	.	.
I	.	.	.	.	.	.
J	.	.	.	.	.	.

. = P > 0.05
* = 0.05 > P > 0.01
** = 0.01 > P > 0.001
*** = 0.001 > P > 0.0001
\+ = Group mortality rate is significantly (0.05 > P > 0.01) lower than that for Group K control.
3AB = 3-Aminobenzamide
NIC = Nicotinamide
NA = Nicotinic Acid

TABLE 3.14. CATEGORICAL MODELLING OF MORTALITY AMONG HD-DOSED GROUPS TO DETECT INHIBITOR LEVEL AND REGIMEN EFFECTS, BY EXPERIMENT

	Target HD Dose					
	LD_{30}			LD_{60}		
Inhibitor:	3AB	NIC	NA	3AB	NIC	NA
Effect						
Inhibitor Level	.	.	.	.	.	.
Inhibitor Regimen	**	.	.	*	.	.
Level-by-Regimen Interaction	*	.	.	.	.	.

. = P > 0.05
* = 0.05 > P > 0.01
** = 0.01 > P > 0.001
3AB = 3-Aminobenzamide
NIC = Nicotinamide
NA = Nicotinic Acid

TABLE 3.15. CATEGORICAL MODELLING OF MORTALITY AMONG HD-DOSED GROUPS TO DETECT THE EFFECT OF TOTAL AMOUNT OF INHIBITOR, BY EXPERIMENT

	Target HD Dose					
	LD_{30}			LD_{60}		
Inhibitor:	3AB	NIC	NA	3AB	NIC	NA
Effect						
Total Inhibitor	*	.	.	.	.	.
Replicate	**	***	*	.	*	***
Total Inhibitor-by-Replicate Interaction	.	.	.	.	.	.

. = P > 0.05
* = 0.05 > P > 0.01
** = 0.01 > P > 0.001
*** = 0.001 > P > 0.0001
3AB = 3-Aminobenzamide
NIC = Nicotinamide
NA = Nicotinic Acid

TABLE 3.16. RAW HEMATOLOGY DATA FOR ALL GROUPS DOSED UNDER MREF PROTOCOL 19 INHIBITOR STUDIES

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = 3AB REPLICATE = 1									
1	B	M93M	8	8	92	<1	0	7.2	0.6
1	B	M32M	10	31	63	<1	<1	6.0	3.0
1	C	M103M	9	9	89	<1	1	8.4	0.8
1	C	M39M	7	5	93	2	0	6.5	0.4
1	D	M11M	2	36	64	1	2	1.2	0.6
1	D	M66M	3	56	43	<1	<1	1.4	1.8
1	E	M133M	2	54	44	<1	2	1.0	1.2
1	E	M69M	2	63	36	<1	1	0.9	1.5
1	F	M38M	4	60	39	<1	6	1.6	2.5
1	F	M110M	4	98	2	<1	1	0.1	3.7
1	G	M33M	3	51	49	1	3	1.3	1.3
1	G	M34M	4	75	25	<1	5	1.0	3.0
1	H	M149M	2	85	15	<1	1	0.4	2.0
1	H	M130M	1	86	13	<1	1	0.2	1.2
1	I	M147M	2	48	51	<1	<1	1.1	1.1
1	I	M124M	6	43	57	1	1	3.6	2.8
1	J	M94M	3	66	34	1	1	1.2	2.2
1	J	M60M	4	92	8	1	1	0.3	3.3
1	K	M139M	2	78	22	1	0	0.4	1.4
1	K	M114M	6	45	53	2	2	3.4	2.9
1	K	M99M	4	74	26	<1	0	1.1	3.1
1	K	M75M	3	34	65	<1	2	2.2	1.2
1	K	M135M	5	68	31	1	1	1.5	3.3
1	K	M51M	4	39	61	<1	2	2.2	1.4
2	B	M80M	11	11	86	<1	<1	9.3	1.2
2	B	M141M	14	32	67	<1	1	9.6	4.6
2	C	M4M	6	14	83	<1	2	5.1	0.9
2	C	M73M	7	6	94	<1	0	6.4	0.4
2	D	M78M	2	59	41	<1	.	1.0	1.4
2	D	M18M	2	39	61	1	.	1.3	0.9
2	E	M125M	5	67	33	1	.	1.6	3.2
2	E	M50M	2	43	56	1	.	1.3	1.0
2	F	M56M	4	87	13	1	.	0.5	3.3
2	F	M36M	2	82	18	1	.	0.4	1.8
2	G	M15M	3	93	7	<1	.	0.2	2.4
2	G	M84M	3	68	32	.	.	0.9	1.9
2	H	M111M	2	53	47	1	.	0.9	1.1
2	H	M117M	3	61	39	1	.	1.0	1.6

Note: See page E-80 for an explanation of the blood parameters.

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
		DOSE = LD_{30} INHIBITOR = 3AB REPLICATE = 1							
2	I	M23M	3	78	22	1	.	0.7	2.3
2	I	M58M	3	31	69	<1	.	2.2	1.0
2	J	M113M	3	45	55	<1	.	1.4	1.2
2	J	M47M	2	45	55	1	.	0.9	0.7
2	K	M37M	4	40	60	<1	.	2.5	1.7
2	K	M31M	2	29	71	<1	.	1.4	0.6
2	K	M19M	3	41	59	<1	.	1.5	1.1
2	K	M22M	3	38	60	<1	.	1.7	1.1
2	K	M101M	7	97	3	<1	.	0.2	7.2
2	K	M52M	2	99	1	<1	<1	0.0	2.2
3	B	M97M	9	8	89	<1	1	7.8	0.7
3	B	M44M	.	4	95	<1	1	.	.
3	C	M128M	6	12	86	1	0	5.5	0.8
3	C	M112M	9	17	83	1	0	7.6	1.6
3	D	M86M	1	14	85	<1	.	0.7	0.1
3	D	M64M	1	24	76	<1	.	1.1	0.3
3	E	M140M	3	15	85	1	.	2.2	0.4
3	E	M134M	0	2	98	<1	.	0.2	0.0
3	F	M72M	1	37	63	2	.	0.4	0.2
3	F	M26M	0	14	86	1	.	0.3	0.1
3	G	M96M	0	17	83	1	.	0.3	0.1
3	G	M55M	0	34	66	1	.	0.3	0.1
3	H	M12M	1	4	96	<1	.	0.8	0.0
3	H	M122M	2	86	14	<1	.	0.3	1.7
3	I	M10M	0	85	15	1	.	0.1	0.3
3	I	M100M	1	28	72	1	.	0.4	0.2
3	J	M121M	1	15	85	1	.	0.7	0.1
3	J	M143M	1	10	90	1	.	1.3	0.1
3	K	M144M	.	21	79	<1	.	.	.
3	K	M127M	0	27	71	<1	.	0.3	0.1
3	K	M104M	0	33	67	1	.	0.3	0.1
3	K	M43M	1	23	77	<1	.	0.9	0.3
3	K	M1M	1	45	55	1	.	0.8	0.6
3	K	M30M	2	31	69	0	.	1.4	0.6
4	B	M102M	8	11	88	1	0	7.2	0.9
4	B	M65M	10	8	90	<1	1	8.6	0.8
4	C	M46M	18	22	76	1	1	13.8	4.0
4	C	M74M	10	8	91	<1	2	9.5	0.8

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
		DOSE = LD_{30} INHIBITOR = 3AB REPLICATE = 1							
4	D	M48M	2	3	97	0	.	2.3	0.1
4	D	M13M	3	9	91	1	.	2.4	0.2
4	E	M6M	1	4	96	1	.	0.6	0.0
4	E	M133M	1	2	97	1	.	1.0	0.0
4	F	M61M	1	3	97	1	.	1.4	0.0
4	F	M16M	1	5	95	<1	.	0.8	0.0
4	G	M118M	0	0	100	<1	.	0.4	0.0
4	G	M42M	1	6	94	1	.	0.6	0.0
4	H	M40M	1	5	95	1	.	1.0	0.1
4	H	M120M	1	3	97	<1	.	0.8	0.0
4	I	M79M	1	0	100	<1	.	0.6	0.0
4	I	M10M	1	3	97	1	.	0.8	0.0
4	J	M88M	2	2	98	<1	.	2.0	0.0
4	J	M5M	2	2	98	1	.	1.8	0.0
4	K	M7M	0	1	99	2	.	0.4	0.0
4	K	M76M	1	0	100	2	.	1.2	0.0
4	K	M53M	2	1	98	<1	.	2.2	0.0
4	K	M62M	2	5	95	<1	.	1.7	0.1
4	K	M29M	0	1	99	<1	.	0.4	0.0
4	K	M25M	1	6	94	<1	.	0.6	0.0
5	B	M70M	4	24	74	<1	0	3.3	1.1
5	B	M93M	7	15	83	1	2	5.6	1.0
5	C	M131M	10	18	80	1	0	7.8	1.8
5	C	M17M	10	12	84	1	1	8.6	1.2
5	D	M71M	3	3	97	1	1	2.7	0.1
5	D	M136M	1	9	91	<1	0	1.1	0.1
5	E	M41M	1	4	96	<1	.	1.0	0.0
5	E	M69M	1	3	97	<1	0	1.0	0.0
5	F	M38M	1	2	97	<1	3	0.8	0.0
5	F	M61M	1	1	99	1	0	1.2	0.0
5	G	M34M	1	0	100	<1	.	0.8	0.0
5	G	M118M	1	2	98	1	.	0.6	0.0
5	H	M111M	0	1	99	1	.	0.4	0.0
5	H	M117M	1	1	99	<1	.	0.6	0.0
5	I	M98M	.	9	91	1	.	.	.
5	I	M119M	1	8	92	<1	.	0.7	0.1
5	J	M113M	1	3	97	1	.	1.0	0.0
5	J	M82M	1	5	95	<1	.	1.3	0.1

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = 3AB REPLICATE = 1									
5	K	M114M	2	3	97	1	4	1.9	0.1
5	K	M37M	2	2	98	<1	.	2.4	0.0
5	K	M75M	2	1	98	1	.	2.2	0.0
5	K	M19M	2	0	100	<1	.	2.4	0.0
5	K	M90M	0	7	93	<1	.	0.4	0.0
5	K	M135M	2	12	88	1	.	1.8	0.2
30	B	M93M	7	9	91	<1	1	6.2	0.6
30	B	M32M	12	17	83	<1	1	10.1	2.1
30	B	M80M	11	8	92	<1	0	10.3	0.9
30	C	M103M	9	7	92	<1	0	8.1	0.6
30	C	M39M	9	13	86	<1	0	7.9	1.2
30	C	M4M	.	65	34	<1	0	.	.
30	D	M11M	12	30	65	<1	0	7.5	3.5
30	D	M66M	9	48	48	<1	0	4.5	4.5
30	D	M78M	7	36	64	<1	0	4.7	2.7
30	E	M133M	4	33	66	<1	1	2.8	1.4
30	E	M69M	6	35	65	<1	0	3.8	2.0
30	E	M125M	11	68	30	1	0	3.3	7.5
30	F	M38M	13	49	46	<1	0	6.0	6.4
30	F	M61M	7	27	72	1	0	4.8	1.8
30	F	M16M	8	45	54	<1	0	4.5	3.8
30	G	M34M	12	40	60	<1	0	7.2	4.8
30	G	M118M	5	59	38	0	0	2.1	3.2
30	H	M111M	9	39	59	<1	1	5.4	3.6
30	H	M12M	8	33	66	1	1	5.4	2.7
30	H	M40M	7	25	74	<1	0	5.0	1.7
30	I	M147M	10	48	52	1	1	5.1	4.7
30	I	M124M	13	39	60	<1	1	7.6	4.9
30	I	M58M	4	20	79	1	<1	3.3	0.8
30	J	M113M	7	27	71	1	0	5.3	2.0
30	J	M47M	4	41	54	<1	0	2.4	1.8
30	J	M143M	6	27	69	1	0	4.3	1.7
30	K	M114M	9	41	56	<1	0	4.9	3.6
30	K	M37M	12	32	66	<1	0	8.2	4.0
30	K	M31M	11	37	61	<1	0	7.0	4.2
30	K	M75M	15	56	43	2	1	6.5	8.4
30	K	M19M	6	32	67	1	1	3.9	1.9
30	K	M22M	12	50	50	<1	0	5.8	5.8

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = 3AB REPLICATE = 1									
30	K	M135M	11	41	55	1	0	6.3	4.7
30	K	M51M	10	46	54	1	0	5.4	4.6
30	K	M1M	10	45	55	<1	0	5.6	4.6

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
		DOSE = LD30 INHIBITOR = 3AB REPLICATE = 2							
1	D	M522M	2	70	29	1	0	0.6	1.5
1	D	M440M	2	77	22	1	1	0.4	1.5
1	E	M406M	5	97	3	1	<1	0.2	5.2
1	E	M437M	2	81	19	1	7	0.5	1.9
1	F	M435M	3	57	36	1	4	0.9	1.5
1	F	M488M	3	41	55	<1	6	1.7	1.2
1	G	M504M	4	56	41	1	3	1.6	2.1
1	G	M520M	3	63	37	<1	3	1.0	1.6
1	H	M426M	3	46	51	1	6	1.5	1.4
1	H	M512M	10	74	26	1	13	2.7	7.7
1	I	M429M	3	75	23	1	2	0.6	2.1
1	I	M513M	8	81	19	<1	1	1.6	6.6
1	J	M438M	3	54	42	1	4	1.2	1.5
1	J	M479M	3	61	37	<1	6	1.3	2.1
1	K	M528M	2	83	17	1	2	0.4	1.8
1	K	M469M	3	70	30	<1	<1	0.8	2.0
1	K	M445M	4	42	58	1	0	2.1	1.5
1	K	M450M	3	63	37	<1	3	1.1	1.9
1	K	M436M	4	73	27	1	2	1.0	2.6
1	K	M483M	.	.	.	.	.	.	.
2	D	M501M	3	65	33	1	.	1.0	2.0
2	D	M463M	2	67	33	<1	.	0.8	1.6
2	E	M506M	2	60	39	<1	.	0.9	1.4
2	E	M415M	3	62	38	2	.	1.1	1.7
2	F	M526M	4	81	18	<1	.	0.7	3.1
2	F	M442M	2	56	44	1	.	0.9	1.1
2	G	M432M	2	81	19	<1	.	0.4	1.8
2	G	M431M	9	83	17	<1	.	1.6	7.8
2	H	M471M	2	71	29	<1	.	0.7	1.7
2	H	M514M	4	60	40	1	.	1.4	2.2
2	I	M525M	4	60	40	<1	31	1.4	2.2
2	I	M524M	3	61	39	<1	36	1.2	1.8
2	J	M456M	2	38	62	<1	.	1.4	0.8
2	J	M511M	2	56	44	0	.	1.1	1.3
2	K	M458M	2	50	50	1	.	1.2	1.2
2	K	M508M	3	76	24	<1	.	0.7	2.3

TABLE 3.16.
(Continued)

DOSE = LD_{30} INHIBITOR = 3AB REPLICATE = 2

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
2	K	M409M	3	42	58	1	31	2.0	1.4
2	K	M493M	6	36	64	<1	.	3.6	2.0
2	K	M503M	.	.	.	.	.	.	.
2	K	M427M	5	53	47	0	32	2.2	2.4
3	D	M497M	1	15	85	3	.	0.7	0.1
3	D	M451M	1	12	88	<1	.	0.5	0.1
3	E	M425M	1	22	78	1	.	0.5	0.1
3	E	M455M	1	9	91	<1	.	0.5	0.1
3	F	M411M	1	42	58	2	.	0.7	0.5
3	F	M401M	1	20	80	1	.	0.8	0.2
3	G	M515M	1	58	42	1	.	0.3	0.3
3	G	M420M	2	20	80	1	.	1.3	0.3
3	H	M475M	0	27	73	1	.	0.3	0.1
3	H	M518M	1	29	71	2	.	0.4	0.2
3	I	M500M	2	33	67	1	.	1.5	0.7
3	I	M449M	1	39	61	1	.	0.5	0.3
3	J	M444M	5	10	90	<1	.	4.1	0.5
3	J	M461M	1	12	87	1	.	0.5	0.1
3	K	M519M	1	26	74	1	.	0.6	0.2
3	K	M430M	1	47	53	1	.	0.7	0.7
3	K	M491M	1	3	97	2	.	1.4	0.0
3	K	M490M	0	17	83	1	.	0.3	0.1
3	K	M465M	0	50	50	1	.	0.2	0.2
3	K	M509M	1	39	61	1	.	0.9	0.5
4	D	M454M	2	2	98	<1	.	1.6	0.0
4	D	M452M	1	3	97	1	.	1.0	0.0
4	E	M441M	1	5	95	<1	.	1.1	0.1
4	E	M459M	1	3	96	1	.	1.2	0.0
4	F	M478M	0	3	97	<1	.	0.4	0.0
4	F	M433M	0	10	90	1	.	0.4	0.0
4	G	M504M	1	2	98	1	.	1.0	0.0
4	G	M434M	5	9	90	1	.	4.9	0.5
4	H	M496M	1	2	98	1	.	0.8	0.0
4	H	M485M	2	4	96	1	.	1.9	0.1
4	I	M499M	0	0	99	<1	.	0.2	0.0
4	I	M464M	0	3	97	<1	.	0.2	0.0
4	J	M448M	2	0	100	2	0	2.0	0.0
4	J	M468M	1	4	96	1	.	0.8	0.0
4	K	M498M	1	5	95	<1	.	1.3	0.1

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = 3AB REPLICATE = 2									
4	K	M521M	0	6	94	1	.	0.4	0.0
4	K	M473M	1	9	91	1	.	0.5	0.1
4	K	M460M	1	1	99	1	.	1.2	0.0
4	K	M484M	2	3	97	<1	.	1.7	0.1
4	K	M527M	2	0	100	<1	.	2.0	0.0
5	D	M416M	3	5	94	3	0	2.4	0.1
5	D	M402M	.	.	.	.	.	.	.
5	E	M516M	.	.	.	.	.	.	.
5	E	M529M	2	7	93	1	.	1.7	0.1
5	F	M495M	1	2	98	<1	.	1.0	0.0
5	F	M446M	1	5	95	<1	.	0.8	0.0
5	G	M520M	1	4	96	2	0	0.6	0.0
5	G	M420M	1	2	98	1	0	1.4	0.0
5	H	M421M	4	7	92	3	1	3.7	0.3
5	H	M428M	1	4	96	1	.	0.8	0.0
5	I	M403M	1	4	96	1	.	0.6	0.0
5	I	M477M	5	2	96	1	0	5.2	0.1
5	J	M404M	.	.	.	.	.	.	.
5	J	M438M	0	5	95	1	.	0.4	0.0
5	K	M423M	.	.	.	.	.	.	.
5	K	M494M	.	.	.	.	.	.	.
5	K	M412M	4	2	98	1	1	4.3	0.1
5	K	M422M	3	1	99	2	1	2.6	0.0
5	K	M436M	0	2	98	<1	.	0.4	0.0
5	K	M503M	1	2	98	<1	.	0.8	0.0
30	D	M522M	9	57	40	<1	0	3.5	5.0
30	D	M501M	6	30	70	<1	0	4.2	1.8
30	D	M463M	11	45	54	<1	1	5.7	4.8
30	E	M506M	12	53	47	1	1	5.7	6.5
30	E	M415M	6	37	61	<1	0	3.9	2.4
30	E	M425M	8	41	57	1	0	4.4	3.2
30	F	M401M	8	36	64	1	0	5.4	3.0
30	F	M488M	5	35	63	<1	0	3.2	1.8
30	F	M442M	10	43	52	<1	0	5.0	4.1
30	G	M504M	8	46	51	2	0	3.9	3.5
30	G	M520M	8	54	43	1	0	3.4	4.2
30	G	M420M	9	39	61	<1	0	5.5	3.5
30	H	M512M	10	35	63	1	0	6.3	3.5
30	H	M514M	8	51	48	<1	1	4.0	4.3

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = 3AB REPLICATE = 2									
30	H	M485M	12	34	62	1	1	7.3	4.0
30	I	M429M	7	40	58	<1	2	4.2	2.9
30	I	M525M	10	35	62	<1	1	6.3	3.6
30	I	M524M	6	37	61	1	2	3.8	2.3
30	J	M438M	10	47	52	2	2	5.1	4.6
30	J	M479M	6	31	66	<1	<1	4.1	1.9
30	J	M456M	5	22	78	1	0	3.9	1.1
30	K	M458M	6	49	49	<1	1	2.8	2.8
30	K	M519M	8	63	36	<1	0	2.7	4.8
30	K	M430M	6	48	50	1	1	2.8	2.7
30	K	M445M	8	34	64	1	0	5.0	2.7
30	K	M450M	6	44	55	<1	0	3.1	2.5
30	K	M409M	7	19	80	<1	1	5.9	1.4
30	K	M436M	11	41	58	1	1	6.6	4.7
30	K	M503M	9	36	64	2	2	5.9	3.3
30	K	M427M	8	37	62	1	0	5.1	3.0

TABLE 3.16.
(Continued)

DOSE = LD_{30} INHIBITOR = NA REPLICATE = 1

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
1	B	M329M	3	15	84	1	0	2.9	0.5
1	B	M229M	5	11	88	1	1	4.8	0.6
1	C	M289M	5	19	76	<1	2	3.8	1.0
1	C	M247M	5	13	85	1	1	4.6	0.7
1	D	M342M	3	60	40	1	4	1.2	1.8
1	D	M258M	6	41	59	<1	7	3.4	2.4
1	E	M285M	3	39	60	1	9	1.7	1.1
1	E	M211M	1	59	41	<1	9	0.6	0.8
1	F	M262M	5	21	77	1	7	4.0	1.1
1	F	M205M	4	29	70	<1	8	2.7	1.1
1	G	M210M	2	40	60	<1	2	1.3	0.9
1	G	M320M	2	70	30	1	7	0.7	1.5
1	H	M341M	4	34	65	<1	7	2.3	1.2
1	H	M236M	2	45	54	1	3	0.9	0.7
1	I	M256M	3	33	67	2	2	1.9	0.9
1	I	M318M	6	38	61	1	5	3.9	2.4
1	J	M312M	6	38	61	2	5	3.9	2.4
1	J	M2001	2	66	33	<1	1	0.6	1.2
1	K	M350M	7	18	80	<1	0	5.3	1.2
1	K	M244M	3	20	79	1	3	2.7	0.7
1	K	M252M	2	73	27	<1	1	0.5	1.3
1	K	M234M	3	38	62	1	2	1.6	1.0
1	K	M260M	3	58	41	1	3	1.1	1.5
1	K	M308M	3	79	21	1	3	0.6	2.2
2	B	M313M	8	19	79	1	0	6.0	1.4
2	B	M294M	6	21	76	1	0	4.6	1.3
2	C	M253M	7	23	76	1	1	5.3	1.6
2	C	M238M	.	.	.	.	.	.	.
2	D	M295M	4	80	20	1	.	0.8	3.2
2	D	M220M	3	37	63	1	.	2.1	1.3
2	E	M202M	3	49	51	1	.	1.4	1.4
2	E	M243M	2	80	20	<1	.	0.3	1.3
2	F	M217M	3	81	19	1	.	0.5	2.3
2	F	M263M	2	73	27	<1	.	0.5	1.3
2	G	M328M	4	21	79	1	.	2.8	0.8
2	H	M346M	3	60	37	1	.	1.0	1.7
2	H	M317M	3	89	11	2	.	0.4	3.0
2	I	M228M	4	45	55	1	.	2.1	1.7
2	I	M304M	3	72	28	<1	.	0.8	2.0

TABLE 3.16.
(Continued)

DOSE = LD_{30} INHIBITOR = NA REPLICATE = 1

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
2	J	M207M	3	61	39	<1	.	1.2	2.0
2	J	M336M	5	54	46	1	.	2.1	2.5
2	K	M335M	3	21	79	1	34	2.4	0.6
2	K	M302M	3	67	33	1	41	1.1	2.1
2	K	M276M	3	25	75	<1	.	2.0	0.7
2	K	M270M	3	82	18	<1	.	0.6	2.6
2	K	M277M	3	72	28	<1	.	0.9	2.3
2	K	M286M	2	76	24	<1	.	0.6	1.8
3	B	M250M	6	11	88	0	0	5.6	0.7
3	B	M303M	6	14	86	<1	1	5.3	0.9
3	C	M330M	8	12	88	<1	0	6.7	0.9
3	C	M298M	9	14	85	<1	0	7.7	1.3
3	D	M241M	1	18	82	1	.	0.7	0.1
3	D	M338M	2	12	88	1	.	1.9	0.3
3	E	M322M	1	7	93	<1	.	0.6	0.0
3	E	M316M	2	8	92	<1	.	2.2	0.2
3	F	M344M	1	5	95	<1	.	1.0	0.1
3	F	M234M	1	5	95	1	.	1.0	0.1
3	G	M321M	2	19	81	<1	.	1.9	0.5
3	G	M351M	3	20	79	1	.	2.2	0.6
3	H	M259M	0	3	97	1	.	0.4	0.0
3	H	M216M	1	2	98	<1	.	0.8	0.0
3	I	M261M	1	6	94	<1	.	1.3	0.1
3	I	M333M	0	.	.	1	.	.	.
3	J	M343M	1	9	91	1	.	0.5	0.1
3	J	M218M	3	12	87	1	.	2.6	0.4
3	K	M349M	1	48	51	<1	.	0.4	0.4
3	K	M269M	2	9	91	<1	.	2.2	0.2
3	K	M225M	2	20	80	1	.	1.4	0.4
3	K	M345M	2	21	79	1	.	1.7	0.5
3	K	M301M	0	6	94	2	.	0.4	0.0
3	K	M299M	2	36	64	<1	.	1.3	0.7
4	B	M347M	8	3	97	1	0	7.4	0.2
4	C	M293M	6	10	89	1	1	5.7	0.6
4	C	M280M	9	9	90	1	0	8.3	0.8
4	D	M227M	3	2	98	1	.	2.5	0.1
4	D	M219M	0	6	94	1	.	0.4	0.0
4	E	M279M	1	4	96	1	.	0.6	0.0
4	E	M306M	2	1	99	<1	.	2.0	0.0

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = NA REPLICATE = 1									
4	F	M245M	1	1	99	<1	.	1.0	0.0
4	F	M296M	2	1	99	<1	.	2.4	0.0
4	G	M351M	2	3	97	<1	2	2.3	0.1
4	G	M210M	1	0	100	1	.	0.8	0.0
4	H	M222M	1	2	98	1	.	1.2	0.0
4	H	M278M	1	4	96	<1	.	1.3	0.1
4	I	M334M	4	4	96	1	.	3.8	0.2
4	I	M256M	2	1	99	1	.	2.0	0.0
4	J	M288M	1	3	97	2	.	1.0	0.0
4	J	M312M	3	7	93	1	.	3.2	0.2
4	K	M269M	0	1	99	2	.	0.4	0.0
4	K	M239M	2	1	99	3	.	2.2	0.0
4	K	M309M	1	3	97	1	.	0.8	0.0
4	K	M319M	6	4	96	<1	3	5.4	0.2
4	K	M308M	1	3	97	<1	.	0.8	0.0
4	K	M248M	0	3	97	1	.	0.2	0.0
5	B	M300M	8	7	88	1	1	7.0	0.6
5	B	M305M	10	4	96	1	1	9.2	0.4
5	C	M284M	7	10	90	<1	1	5.9	0.7
5	C	M339M	10	8	90	1	0	8.6	0.8
5	D	M342M	0	13	87	1	0	0.3	0.1
5	D	M258M	3	2	98	1	1	3.1	0.1
5	E	M215M	1	0	100	1	1	1.0	0.0
5	E	M285M	1	3	97	<1	1	1.0	0.0
5	F	M205M	1	1	99	<1	0	1.4	0.0
5	F	M234M	0	2	98	1	.	0.4	0.0
5	G	M266M	0	1	99	1	.	0.4	0.0
5	G	M328M	2	3	97	1	3	1.7	0.1
5	H	M281M	2	2	98	1	1	2.4	0.0
5	H	M208M	1	0	100	<1	.	1.0	0.0
5	I	M318M	4	6	94	4	2	3.4	0.2
5	I	M228M	1	1	99	<1	.	0.8	0.0
5	J	M209M	0	0	100	<1	.	0.4	0.0
5	J	M207M	1	1	99	1	.	1.0	0.0
5	K	M314M	1	1	99	1	.	0.6	0.0
5	K	M244M	3	0	100	2	.	2.6	0.0
5	K	M254M	1	1	99	1	2	1.0	0.0
5	K	M276M	1	2	98	1	.	1.4	0.0
5	K	M286M	0	0	100	<1	.	0.4	0.0

TABLE 3.16.
(Continued)

DOSE = LD_{30} INHIBITOR = NA REPLICATE = 1

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
5	K	M299M	1	2	98	2	.	1.4	0.0
30	B	M329M	4	11	89	1	2	3.5	0.4
30	B	M229M	4	9	90	<1	0	3.7	0.4
30	B	M313M	3	11	89	1	0	2.9	0.4
30	C	M289M	5	10	90	<1	0	4.2	0.5
30	C	M247M	4	13	87	<1	0	3.8	0.6
30	C	M253M	6	15	82	<1	2	4.6	0.8
30	D	M342M	11	79	19	<1	0	2.0	8.5
30	D	M258M	.	9	90	<1	1	.	.
30	D	M220M	3	47	53	<1	0	1.6	1.5
30	E	M285M	5	26	71	1	0	3.3	1.2
30	E	M202M	4	33	66	1	2	2.3	1.2
30	E	M211M	3	41	57	<1	0	1.9	1.4
30	F	M262M	8	27	72	2	1	5.7	2.1
30	F	M205M	6	26	73	1	1	4.4	1.6
30	G	M328M	4	57	41	<1	0	1.6	2.3
30	G	M210M	5	20	80	<1	0	3.8	1.0
30	G	M321M	6	41	59	<1	0	3.8	2.6
30	H	M341M	4	21	77	1	0	3.3	0.9
30	H	M236M	6	56	44	<1	1	2.6	3.4
30	H	M222M	4	28	71	1	0	2.7	1.1
30	I	M256M	4	76	23	<1	1	1.0	3.3
30	I	M318M	6	20	80	0	0	5.1	1.3
30	I	M261M	3	16	80	0	1	2.2	0.4
30	J	M312M	6	29	66	<1	1	4.2	1.8
30	J	M207M	6	40	59	<1	0	3.8	2.6
30	J	M336M	.	51	48	1	1	.	.
30	K	M350M	4	16	83	0	1	2.9	0.6
30	K	M244M	6	21	76	<1	2	4.3	1.2
30	K	M335M	4	16	84	1	2	3.4	0.6
30	K	M254M	5	30	64	1	0	2.9	1.4
30	K	M276M	5	14	86	1	2	4.0	0.7
30	K	M225M	4	19	80	2	0	3.1	0.7
30	K	M308M	4	48	51	2	1	2.2	2.1
30	K	M286M	3	28	66	1	0	1.7	0.7
30	K	M299M	2	45	55	2	1	1.0	0.8

TABLE 3.16.
(Continued)

DOSE = LD_{30} INHIBITOR = NA REPLICATE = 2

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
1	D	M808M	.	38	60	<1	4	.	.
1	D	M853M	.	35	63	<1	3	.	.
1	E	M906M	.	55	44	<1	2	.	.
1	E	M890M	.	41	59	<1	6	.	.
1	F	M912M	.	25	75	<1	0	.	.
1	F	M919M	.	37	61	<1	3	.	.
1	G	M830M	.	54	43	<1	3	.	.
1	G	M924M	.	69	31	<1	4	.	.
1	H	M858M	.	29	68	1	3	.	.
1	H	M941M	.	36	62	<1	2	.	.
1	I	M823M	.	31	68	<1	4	.	.
1	I	M832M	.	76	24	<1	2	.	.
1	J	M824M	.	37	62	1	2	.	.
1	J	M877M	.	57	39	1	4	.	.
1	K	M907M	.	70	29	1	4	.	.
1	K	M831M	.	53	47	<1	2	.	.
1	K	M899M	.	53	47	<1	1	.	.
1	K	M927M	.	42	58	<1	4	.	.
1	K	M944M	.	70	27	<1	1	.	.
2	D	M935M	.	36	64	<1	.	.	.
2	D	M859M	.	57	43	<1	.	.	.
2	E	M829M	.	73	27	<1	.	.	.
2	E	M937M	.	59	41	2	.	.	.
2	F	M881M	.	66	33	1	.	.	.
2	F	M946M	.	43	57	1	.	.	.
2	G	M923M	.	47	53	<1	.	.	.
2	G	M854M	.	57	43	1	.	.	.
2	H	M940M	.	27	72	1	.	.	.
2	H	M810M	.	16	83	<1	.	.	.
2	I	M821M	.	66	32	<1	.	.	.
2	I	M883M	.	56	43	1	.	.	.
2	J	M932M	.	55	42	1	9	.	.
2	J	M842M	.	25	75	<1	.	.	.
2	K	M815M	.	41	59	<1	.	.	.
2	K	M835M	.	82	18	1	.	.	.
2	K	M828M	.	48	52	<1	.	.	.
2	K	M822M	.	58	42	<1	.	.	.
2	K	M806M	.	38	62	1	.	.	.
2	K	M836M	.	51	49	<1	13	.	.

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = NA REPLICATE = 2									
3	D	M934M	.	20	80	1	.	.	.
3	D	M847M	.	36	64	1	.	.	.
3	E	M852M	.	5	95	1	.	.	.
3	E	M897M	.	21	78	1	.	.	.
3	F	M809M	.	17	83	0	.	.	.
3	F	M916M	.	12	88	1	.	.	.
3	G	M860M	.	31	69	<1	.	.	.
3	G	M903M	.	18	82	<1	.	.	.
3	H	M816M	.	26	74	<1	.	.	.
3	H	M817M	.	14	86	2	.	.	.
3	I	M895M	.	28	72	1	.	.	.
3	I	M893M	.	32	68	<1	.	.	.
3	J	M825M	.	14	86	1	.	.	.
3	J	M896M	.	13	87	1	2	.	.
3	K	M848M	.	45	55	<1	.	.	.
3	K	M804M	.	13	87	<1	.	.	.
3	K	M813M	.	40	60	1	.	.	.
3	K	M846M	.	18	82	1	.	.	.
3	K	M841M	.	16	84	1	.	.	.
3	K	M880M	.	8	92	2	.	.	.
4	D	M894M	.	3	97	1	.	.	.
4	D	M902M	.	0	100	1	.	.	.
4	E	M917M	.	0	100	<1	.	.	.
4	E	M814M	.	2	98	<1	.	.	.
4	F	M930M	.	2	97	2	2	.	.
4	F	M851M	.	6	94	1	.	.	.
4	G	M913M	.	3	97	1	.	.	.
4	G	M918M	.	4	96	<1	.	.	.
4	H	M943M	.	8	92	<1	1	.	.
4	H	M805M	.	6	94	<1	.	.	.
4	I	M827M	.	5	95	<1	.	.	.
4	I	M915M	.	3	97	<1	.	.	.
4	J	M838M	.	9	91	1	.	.	.
4	J	M892M	.	1	99	<1	.	.	.
4	K	M826M	.	3	97	<1	.	.	.
4	K	M939M	.	1	97	<1	.	.	.
4	K	M905M	.	13	87	1	.	.	.
4	K	M911M	.	5	94	<1	.	.	.

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = NA REPLICATE = 2									
4	K	M803M	.	12	88	1	.	.	.
4	K	M945M	.	3	97	<1	.	.	.
5	D	M802M	4	9	91	1	0	3.6	0.4
5	D	M938M	3	5	95	<1	0	2.7	0.1
5	E	M814M	3	1	99	<1	0	3.0	0.0
5	E	M850M	1	5	95	<1	.	0.6	0.0
5	F	M837M	3	8	92	1	1	2.4	0.2
5	F	M849M	1	7	93	0	.	0.7	0.1
5	G	M876M	1	0	100	<1	.	0.8	0.0
5	G	M830M	1	3	97	<1	.	1.4	0.0
5	H	M891M	1	2	97	1	.	1.4	0.0
5	H	M858M	3	13	87	2	1	3.0	0.4
5	I	M820M	1	2	98	1	.	0.8	0.0
5	J	M845M	1	5	94	1	.	1.1	0.1
5	J	M824M	2	2	98	2	3	1.8	0.0
5	K	M933M	0	1	98	<1	.	0.4	0.0
5	K	M904M	2	4	96	1	0	1.9	0.1
5	K	M857M	2	4	96	1	0	2.1	0.1
5	K	M899M	1	1	99	<1	.	1.2	0.0
5	K	M819M	1	3	97	0	.	1.2	0.0
5	K	M898M	3	2	98	1	.	3.1	0.1
30	D	M808M	10	43	56	2	0	5.4	4.1
30	D	M853M	10	30	70	1	1	7.1	3.1
30	D	M935M	.	51	49	<1	0	.	.
30	E	M906M	7	34	62	<1	1	4.2	2.3
30	E	M890M	18	47	51	1	0	9.2	8.5
30	E	M937M	12	55	42	<1	0	5.0	6.6
30	F	M912M	5	32	65	2	1	3.5	1.7
30	F	M919M	9	53	46	<1	0	4.3	5.0
30	F	M946M	9	49	51	2	0	4.8	4.6
30	G	M830M	15	25	72	<1	0	10.9	3.8
30	G	M923M	22	61	38	<1	0	8.2	13.2
30	G	M854M	7	34	66	1	1	4.9	2.5
30	H	M858M	16	31	68	<1	0	11.0	5.0
30	H	M940M	14	35	64	<1	0	9.1	5.0
30	H	M941M	2	56	43	<1	0	1.0	1.3
30	I	M823M	6	46	51	1	0	2.9	2.6
30	I	M895M	14	49	50	1	0	6.8	6.7

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = NA REPLICATE = 2									
30	I	M893M	6	42	55	1	1	3.4	2.6
30	J	M824M	13	43	55	<1	0	7.3	5.7
30	J	M932M	.	.	.	.	.	.	.
30	J	M842M	8	47	52	<1	1	4.3	3.9
30	K	M831M	2	23	77	1	0	1.7	0.5
30	K	M815M	12	71	28	<1	0	3.5	8.8
30	K	M826M	8	49	50	<1	1	4.2	4.1
30	K	M922M	10	81	17	<1	0	1.7	7.9
30	K	M828M	7	47	51	1	0	3.4	3.1
30	K	M813M	7	44	55	<1	0	4.1	3.3
30	K	M927M	7	31	67	1	0	4.6	2.1
30	K	M944M	5	29	69	0	0	3.7	1.6
30	K	M806M	10	37	62	0	1	6.1	3.6

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = NIC REPLICATE = 1									
1	B	M019M	6	24	74	1	3	4.3	1.4
1	B	M098M	6	16	83	1	1	4.8	0.9
1	C	M080M	6	28	71	1	2	4.4	1.7
1	C	M021M	8	13	87	1	1	6.8	1.0
1	D	M088M	4	83	16	2	3	0.7	3.7
1	D	M114M	3	70	30	1	0	0.8	2.0
1	E	M020M	5	69	31	<1	0	1.6	3.6
1	E	M059M	4	53	45	1	2	1.9	2.2
1	F	M041M	3	93	7	1	1	0.2	2.8
1	G	M068M	3	90	9	<1	2	0.3	2.5
1	G	M118M	3	93	7	<1	0	0.2	2.8
1	H	M064M	6	92	8	2	1	0.5	5.7
1	H	M043M	5	87	12	1	1	0.6	4.5
1	I	M117M	4	95	5	<1	0	0.2	3.6
1	I	M096M	5	85	15	<1	0	0.8	4.3
1	J	M052M	6	72	28	3	1	1.7	4.5
1	J	M030M	4	95	5	1	1	0.2	3.4
1	K	M108M	2	86	14	<1	1	0.3	2.1
1	K	M095M	6	82	18	1	0	1.1	5.1
2	B	M032M	8	30	66	1	2	5.5	2.5
2	B	M009M	5	25	74	<1	0	4.0	1.4
2	C	M065M	12	29	69	<1	0	8.3	3.5
2	D	M124M	5	95	5	1	2	0.2	4.6
2	D	M008M	2	88	10	<1	26	0.2	2.1
2	E	M071M	5	77	23	<1	.	1.2	4.0
2	E	M004M	2	93	7	1	.	0.2	2.2
2	F	M074M	3	79	21	1	.	0.6	2.2
2	G	M125M	3	42	58	1	.	1.7	1.3
2	G	M053M	2	90	10	1	0	0.2	1.4
2	H	M033M	4	88	12	<1	.	0.4	3.2
2	H	M102M	3	99	1	1	.	0.0	3.2
2	I	M018M	3	73	27	1	.	0.7	1.9
2	I	M082M	5	95	5	<1	.	0.3	4.8
2	J	M012M	2	59	41	1	.	1.0	1.4
2	J	M005M	3	78	22	1	.	0.6	2.2
2	K	M120M	2	43	55	1	.	1.1	0.9
3	B	M029M	10	32	68	<1	0	7.1	3.3
3	B	M063M	7	33	66	1	2	4.9	2.4
3	C	M023M	9	19	81	<1	0	7.6	1.8

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = NIC REPLICATE = 1									
3	C	M087M	5	21	77	1	0	3.5	1.0
3	D	M119M	0	19	81	1	.	0.3	0.1
3	D	M104M	1	13	87	<1	.	0.7	0.1
3	E	M103M	1	16	84	<1	.	0.5	0.1
3	E	M066M	1	10	90	2	.	0.5	0.1
3	F	M011M	0	45	55	<1	.	0.1	0.1
3	F	M031M	0	36	64	<1	.	0.1	0.1
3	G	M003M	1	14	86	1	.	0.5	0.1
3	G	M056M	3	57	43	1	.	1.1	1.5
3	H	M014M	1	62	38	<1	.	0.4	0.6
3	H	M101M	0	10	90	1	.	0.4	0.0
3	I	M093M	8	50	50	1	1	3.9	3.9
3	I	M015M	0	51	48	<1	.	0.2	0.2
3	J	M084M	3	48	52	<1	.	1.6	1.4
3	J	M091M	1	30	70	1	.	0.7	0.3
3	K	M079M	1	70	30	<1	.	0.2	0.6
3	K	M025M	1	58	42	<1	.	0.3	0.5
4	B	M013M	9	14	84	<1	0	7.4	1.2
4	B	M116M	7	27	71	1	0	5.1	1.9
4	C	M010M	10	22	75	<1	0	7.7	2.2
4	C	M100M	16	32	67	<1	1	11.0	5.2
4	D	M099M	0	22	78	<1	.	0.3	0.1
4	D	M088M	1	8	92	<1	.	0.6	0.0
4	E	M109M	0	38	62	1	.	0.1	0.1
4	E	M103M	1	2	98	<1	.	0.8	0.0
4	F	M016M	1	12	88	<1	.	0.5	0.1
4	F	M042M	2	18	82	1	.	1.3	0.3
4	G	M024M	3	14	86	<1	.	2.6	0.4
4	G	M002M	0	2	98	<1	.	0.4	0.0
4	H	M122M	1	9	91	<1	.	0.5	0.1
4	H	M022M	0	18	82	0	.	0.3	0.1
4	I	M046M	0	12	88	<1	.	0.2	0.0
4	I	M049M	1	65	35	<1	.	0.2	0.4
4	J	M115M	1	11	89	<1	.	1.2	0.2
4	J	M060M	0	13	87	1	.	0.3	0.1
4	K	M058M	1	11	89	1	.	0.5	0.1
4	K	M026M	0	29	71	<1	.	0.3	0.1
5	B	M055M	8	15	83	<1	0	6.3	1.1

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
		DOSE = LD_{30} INHIBITOR = NIC REPLICATE = 1							
5	B	M019M	8	19	80	<1	0	6.7	1.6
5	C	M094M	7	12	84	<1	1	5.5	0.8
5	C	M038M	17	36	64	<1	0	10.6	6.0
5	D	M008M	1	10	90	<1	0	0.7	0.1
5	D	M088M	0	11	89	1	0	0.4	0.0
5	E	M059M	2	3	97	1	2	1.6	0.0
5	E	M071M	1	6	93	<1	.	0.6	0.0
5	F	M036M	1	4	96	1	.	0.8	0.0
5	F	M074M	0	8	91	<1	.	0.4	0.0
5	G	M027M	2	2	98	<1	0	1.6	0.0
5	G	M056M	1	6	93	<1	1	0.6	0.0
5	H	M112M	2	1	99	1	2	1.6	0.0
5	H	M070M	0	4	96	1	.	0.4	0.0
5	I	M107M	0	7	92	1	.	0.2	0.0
5	I	M117M	0	17	83	<1	.	0.2	0.0
5	J	M060M	0	5	95	1	.	0.4	0.0
5	J	M113M	4	10	90	1	1	3.2	0.4
5	K	M120M	1	6	94	1	.	0.8	0.0
5	K	M025M	1	13	87	1	.	0.5	0.1
30	B	M019M	11	19	78	1	1	8.7	2.1
30	B	M098M	5	20	78	<1	1	4.2	1.1
30	B	M032M	7	21	74	1	2	5.0	1.4
30	C	M080M	7	21	79	1	<1	5.8	1.6
30	C	M021M	13	14	84	<1	0	11.1	1.8
30	C	M065M	9	37	63	<1	0	5.5	3.3
30	D	M088M	6	61	38	2	0	2.4	3.8
30	D	M008M	8	40	60	1	1	4.7	3.1
30	D	M119M	7	51	48	1	0	3.5	3.7
30	E	M059M	10	39	60	<1	0	6.2	4.1
30	E	M071M	4	39	61	<1	0	2.3	1.5
30	E	M103M	6	54	44	<1	0	2.8	3.5
30	F	M097M	5	40	60	<1	0	2.8	1.8
30	F	M074M	7	61	38	<1	1	2.5	4.0
30	F	M034M	13	65	34	1	1	4.4	8.5
30	G	M118M	5	47	51	<1	0	2.3	2.2
30	G	M125M	7	40	59	1	0	3.9	2.6
30	G	M003M	17	59	39	1	0	6.6	10.0
30	H	M064M	8	41	58	<1	1	4.5	3.2
30	H	M043M	9	52	48	<1	0	4.4	4.8

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = NIC REPLICATE = 1									
30	H	M033M	15	74	26	1	0	3.9	11.1
30	I	M018M	2	42	56	1	0	1.2	0.9
30	I	M093M	10	45	54	<1	0	5.4	4.5
30	J	M052M	7	33	67	1	0	4.4	2.2
30	J	M012M	4	47	50	<1	0	1.9	1.8
30	J	M084M	9	34	63	<1	<1	5.5	3.0
30	K	M120M	7	52	43	1	0	2.9	3.5
30	K	M025M	.	66	34	1	0	.	.
30	K	M058M	7	30	65	<1	1	4.8	2.2

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = NIC REPLICATE = 2									
1	D	M085M	3	54	45	1	1	1.4	1.6
1	D	M092M	4	62	37	<1	2	1.5	2.5
1	E	M044M	7	61	38	1	2	2.7	4.4
1	E	M093M	7	59	41	<1	4	2.8	4.0
1	F	M103M	4	78	22	1	2	0.8	3.0
1	F	M122M	3	59	40	<1	5	1.2	1.8
1	G	M037M	3	79	19	<1	2	0.5	2.1
1	G	M032M	5	66	31	<1	0	1.6	3.3
1	H	M019M	6	31	65	<1	2	3.6	1.7
1	H	M109M	2	93	7	1	3	0.2	2.0
1	I	M120M	6	66	33	1	1	2.0	4.0
1	I	M011M	3	56	43	1	2	1.3	1.7
1	J	M003M	4	56	43	1	1	1.5	2.0
1	J	M005M	8	67	33	<1	3	2.8	5.6
1	K	M076M	3	42	56	<1	0	1.6	1.2
1	K	M089M	5	48	52	1	2	2.4	2.2
2	D	M070M	3	82	18	<1	.	0.6	2.8
2	D	M025M	3	59	41	1	.	1.4	2.0
2	E	M066M	5	80	20	<1	.	1.0	3.8
2	E	M033M	3	27	73	1	.	2.0	0.8
2	F	M119M	4	80	20	<1	.	0.8	3.0
2	F	M082M	2	76	24	1	.	0.6	1.8
2	G	M086M	4	53	47	1	.	2.1	2.3
2	G	M039M	6	82	18	<1	.	1.0	4.6
2	H	M014M	5	34	66	<1	.	3.0	1.6
2	H	M001M	5	37	62	1	44	2.9	1.7
2	I	M028M	4	63	36	1	54	1.3	2.3
2	I	M056M	3	63	36	2	.	1.2	2.0
2	J	M105M	4	40	58	<1	.	2.1	1.4
2	J	M020M	5	26	71	3	29	3.8	1.4
2	K	M104M	4	42	58	1	.	2.2	1.6
2	K	M010M	4	49	51	<1	.	2.1	2.1
3	D	M117M	1	52	48	1	.	0.7	0.7
3	D	M064M	1	10	90	1	.	0.7	0.1
3	E	M124M	2	38	62	<1	.	1.2	0.8
3	E	M069M	3	28	72	<1	.	2.0	0.8
3	F	M040M	4	60	40	1	.	1.8	2.6
3	F	M047M	1	37	63	<1	.	0.8	0.4
3	G	M007M	1	19	81	1	.	0.5	0.1

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{30} INHIBITOR = NIC REPLICATE = 2									
3	G	M068M	1	21	79	1	.	0.6	0.2
3	H	M021M	4	36	64	<1	.	2.8	1.6
3	H	M013M	1	34	66	<1	.	0.9	0.5
3	I	M061M	7	49	51	<1	.	3.5	3.3
3	I	M035M	3	40	60	<1	.	1.9	1.3
3	J	M046M	2	28	72	1	.	1.7	0.7
3	J	M090M	5	54	46	<1	.	2.2	2.6
3	K	M077M	2	31	69	1	.	1.7	0.7
3	K	M073M	2	83	17	1	.	0.4	1.8
4	D	M052M	1	5	95	1	.	0.6	0.0
4	D	M088M	1	8	92	<1	.	0.7	0.1
4	E	M100M	1	7	93	<1	.	0.7	0.1
4	E	M060M	1	19	81	1	.	0.8	0.2
4	F	M102M	3	9	91	2	2	3.1	0.3
4	F	M027M	1	13	87	<1	.	1.2	0.2
4	G	M118M	1	4	96	<1	.	0.8	0.0
4	G	M058M	1	6	94	1	.	1.3	0.1
4	H	M123M	1	2	98	1	.	1.2	0.0
4	H	M096M	3	11	89	<1	1	2.3	0.3
4	I	M084M	10	31	68	2	1	6.8	3.1
4	I	M098M	0	15	85	<1	.	0.3	0.1
4	J	M015M	2	9	91	<1	.	2.0	0.2
4	J	M078M	2	20	80	<1	.	1.3	0.3
4	K	M023M	0	4	96	1	.	0.4	0.0
4	K	M110M	1	5	95	1	.	0.8	0.0
5	D	M074M	3	2	98	1	0	3.1	0.1
5	D	M053M	1	2	98	1	.	0.6	0.0
5	E	M018M	0	0	100	<1	0	0.2	0.0
5	E	M099M	1	5	95	1	0	1.0	0.1
5	F	M017M	5	14	86	1	1	4.3	0.7
5	F	M009M	4	15	85	1	1	3.4	0.6
5	G	M042M	2	3	97	<1	.	1.6	0.0
5	G	M107M	0	2	98	1	.	0.4	0.0
5	H	M097M	1	7	93	<1	.	0.7	0.1
5	H	M048M	0	15	85	<1	.	0.3	0.1
5	I	M067M	2	4	96	1	0	1.7	0.1
5	I	M044M	1	7	92	2	1	1.1	0.1
5	J	M006M	3	10	90	<1	0	2.3	0.3
5	J	M026M	1	3	97	<1	0	0.8	0.0

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
		DOSE = LD_{30} INHIBITOR = NIC REPLICATE = 2							
5	K	M049M	0	1	99	<1	.	0.2	0.0
5	K	M037M	0	8	92	<1	.	0.4	0.0
30	D	M085M	9	23	77	1	1	7.2	2.2
30	D	M092M	16	32	66	<1	1	10.6	5.1
30	D	M070M	11	62	38	<1	1	4.3	7.1
30	E	M044M	12	39	60	<1	0	7.0	4.5
30	E	M093M	23	27	73	<1	0	16.6	6.2
30	E	M066M	11	23	74	<1	<1	7.8	2.4
30	F	M103M	13	51	48	<1	1	6.1	6.5
30	F	M122M	7	25	72	<1	0	5.3	1.9
30	F	M119M	9	36	63	<1	0	5.9	3.4
30	G	M032M	10	14	81	1	2	8.3	1.4
30	G	M086M	8	30	69	<1	0	5.5	2.4
30	G	M039M	11	42	58	<1	1	6.1	4.5
30	H	M019M	11	23	70	<1	0	7.6	2.5
30	H	M014M	17	33	62	<1	0	10.4	5.5
30	H	M001M	15	45	53	1	0	8.0	6.8
30	I	M120M	15	50	50	1	0	7.6	7.6
30	I	M011M	7	37	63	<1	0	4.7	2.7
30	I	M028M	9	44	55	<1	0	5.0	4.0
30	J	M003M	11	46	51	1	0	5.4	4.9
30	J	M005M	.	30	68	<1	0	.	.
30	J	M105M	6	25	71	<1	0	4.4	1.6
30	K	M089M	11	24	74	1	1	7.8	2.5
30	K	M104M	11	15	83	2	1	8.8	1.6
30	K	M010M	10	17	82	<1	0	8.4	1.7

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = 3AB REPLICATE = 1									
1	A	M737M	9	31	68	1	0	6.0	2.7
1	A	M692M	9	17	82	1	1	7.1	1.5
1	B	M615M	5	9	89	1	0	4.8	0.5
1	B	M723M	8	15	82	1	1	6.4	1.2
1	C	M731M	12	15	83	<1	0	9.8	1.8
1	C	M686M	10	6	92	<1	0	9.2	0.6
1	D	M638M	2	87	12	1	2	0.3	1.9
1	D	M671M	7	93	7	<1	0	0.5	6.9
1	E	M630M	3	62	36	<1	0	1.2	2.0
1	E	M707M	4	80	20	1	3	0.8	3.4
1	F	M642M	2	46	51	<1	3	1.2	1.1
1	F	M696M	2	73	26	<1	0	0.6	1.8
1	G	M685M	7	94	6	1	0	0.4	6.2
1	G	M657M	2	72	28	<1	<1	0.7	1.7
1	H	M746M	4	52	48	1	1	2.0	2.2
1	H	M604M	4	57	43	1	0	1.5	2.1
1	I	M729M	2	45	52	0	0	1.0	0.9
1	I	M699M	3	47	52	1	1	1.7	1.5
1	J	M670M	3	77	20	1	0	0.7	2.6
1	J	M647M	3	61	38	<1	<1	1.1	1.8
1	K	M734M	4	19	80	1	0	3.2	0.8
1	K	M722M	11	98	2	<1	0	0.2	10.8
1	K	M720M	3	79	21	<1	0	0.7	2.5
1	K	M725M	2	82	17	1	0	0.3	1.5
1	K	M744M	3	42	57	<1	1	1.8	1.3
1	K	M645M	4	64	34	<1	1	1.2	2.3
2	A	M703M	11	24	74	1	1	7.8	2.5
2	A	M741M	17	44	54	1	0	9.0	7.3
2	B	M643M	9	4	96	<1	1	8.4	0.4
2	B	M742M	10	14	84	<1	<1	8.7	1.5
2	C	M651M	14	21	78	<1	0	10.8	2.9
2	C	M739M	11	9	90	1	0	9.7	1.0
2	D	M606M	3	80	19	<1	.	0.6	2.6
2	D	M752M	3	60	40	1	.	1.2	1.8
2	E	M728M	4	49	50	1	.	1.9	1.9
2	E	M727M	3	65	35	1	.	1.1	2.0
2	F	M726M	2	53	45	1	.	1.1	1.3
2	F	M608M	1	87	5	<1	0	0.1	1.0
2	G	M627M	3	39	61	1	.	1.8	1.2

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
		DOSE = LD_{60} INHIBITOR = 3AB REPLICATE = 1							
2	G	M716M	4	79	21	<1	.	0.8	2.8
2	H	M612M	2	63	37	<1	.	0.8	1.4
2	H	M619M	7	88	12	<1	.	0.9	6.3
2	I	M616M	3	85	15	<1	.	0.5	2.7
2	I	M755M	3	73	27	<1	15	0.8	2.2
2	J	M677M	3	54	46	<1	.	1.5	1.7
2	J	M730M	5	29	71	<1	.	3.8	1.6
2	K	M668M	4	61	39	<1	.	1.4	2.2
2	K	M649M	4	65	34	<1	.	1.3	2.5
2	K	M695M	4	59	41	1	.	1.5	2.1
2	K	M754M	3	53	46	<1	.	1.6	1.8
2	K	M691M	3	47	53	1	.	1.6	1.4
2	K	M631M	3	66	34	1	.	1.0	2.0
3	A	M601M	12	12	85	<1	0	10.0	1.4
3	A	M605M	8	1	96	<1	0	7.7	0.1
3	B	M632M	8	12	87	<1	1	6.6	0.9
3	B	M672M	9	21	78	0	0	7.0	1.9
3	C	M635M	9	8	87	<1	0	7.8	0.7
3	C	M663M	7	20	79	1	0	5.4	1.4
3	D	M748M	2	44	56	<1	.	0.9	0.7
3	D	M679M	1	40	60	1	.	0.4	0.2
3	E	M613M	1	7	93	1	.	0.9	0.1
3	E	M697M	1	4	96	1	.	1.2	0.0
3	F	M602M	1	34	66	<1	.	0.4	0.2
3	F	M704M	1	25	75	0	.	0.8	0.3
3	G	M698M	1	3	97	0	.	1.0	0.0
3	G	M682M	0	55	45	<1	.	0.2	0.2
3	H	M644M	1	6	94	1	.	1.1	0.1
3	H	M747M	0	26	74	1	.	0.3	0.1
3	I	M681M	2	80	20	1	.	0.4	1.8
3	I	M740M	1	15	85	1	.	0.9	0.2
3	J	M669M	2	39	61	<1	.	1.0	0.5
3	J	M660M	3	14	86	1	.	2.2	0.4
3	K	M719M	2	2	98	<1	.	1.6	0.0
3	K	M680M	0	10	90	1	.	0.4	0.0
3	K	M736M	1	42	58	<1	.	0.3	0.3
3	K	M662M	1	19	81	<1	.	0.5	0.1
3	K	M629M	3	9	91	1	.	2.7	0.3
3	K	M610M	3	35	65	<1	.	1.7	0.9

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
		DOSE = LD_{60} INHIBITOR = 3AB REPLICATE = 1							
3	K	M713M	2	46	54	1	.	1.1	0.9
4	A	M517M	6	14	85	0	0	5.3	0.9
4	A	M743M	6	12	85	1	0	5.3	0.7
4	B	M640M	7	19	81	<1	0	5.7	1.3
4	B	M693M	9	19	80	1	1	7.4	1.7
4	C	M666M	8	7	92	<1	0	7.4	0.6
4	C	M665M	8	19	81	<1	0	6.5	1.5
4	D	M702M	0	4	96	<1	.	0.4	0.0
4	D	M753M	3	21	79	<1	.	2.2	0.6
4	E	M751M	2	6	94	1	.	1.5	0.1
4	E	M749M	1	6	94	<1	.	1.1	0.1
4	F	M618M	1	5	95	<1	.	0.6	0.0
4	F	M721M	0	2	98	1	.	0.4	0.0
4	G	M705M	0	1	99	1	.	0.4	0.0
4	G	M603M	0	5	95	<1	.	0.4	0.0
4	H	M676M	1	3	96	<1	.	0.6	0.0
4	H	M709M	0	2	98	<1	.	0.4	0.0
4	I	M624M	3	7	93	<1	.	3.2	0.2
4	I	M652M	2	6	94	<1	.	2.3	0.1
4	J	M678M	3	3	97	2	.	2.7	0.1
4	J	M607M	1	5	95	1	.	1.1	0.1
4	K	M757M	1	3	97	<1	.	0.8	0.0
4	K	M623M	0	13	86	<1	.	0.3	0.1
4	K	M733M	2	5	95	0	.	2.1	0.1
4	K	M725M	1	8	92	<1	.	0.9	0.1
4	K	M648M	1	2	98	1	.	1.0	0.0
4	K	M738M	3	4	96	1	.	3.1	0.1
5	A	M654M	9	14	84	1	2	7.2	1.2
5	A	M712M	10	15	84	<1	0	8.2	1.5
5	B	M689M	8	24	75	0	<1	6.0	1.9
5	B	M688M	8	19	80	<1	0	6.2	1.5
5	C	M675M	8	21	76	<1	0	6.2	1.7
5	C	M637M	7	6	93	<1	1	6.3	0.4
5	D	M724M	0	4	96	<1	.	0.4	0.0
5	D	M752M	0	9	91	1	.	0.4	0.0
5	E	M655M	3	2	98	<1	.	2.9	0.1
5	E	M613M	1	1	99	<1	0	1.2	0.0
5	F	M618M	1	1	99	0	.	1.0	0.0
5	F	M642M	2	12	88	<1	0	1.9	0.3

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
		DOSE = LD_{60} INHIBITOR = 3AB REPLICATE = 1							
5	G	M627M	1	0	100	0	.	1.2	0.0
5	H	M706M	1	1	99	<1	.	0.6	0.0
5	H	M709M	1	0	100	0	.	0.6	0.0
5	I	M729M	1	0	100	<1	.	0.6	0.0
5	I	M755M	2	0	100	<1	1	2.0	0.0
5	J	M607M	0	3	97	1	.	0.4	0.0
5	J	M730M	1	1	99	1	.	1.2	0.0
5	K	M734M	2	1	99	1	1	2.2	0.0
5	K	M719M	0	0	100	1	.	0.4	0.0
5	K	M733M	1	3	97	1	.	1.4	0.0
5	K	M695M	.	1	99	<1	.	.	.
5	K	M713M	1	1	99	1	.	1.0	0.0
30	A	M737M	10	34	65	1	0	6.5	3.4
30	A	M692M	7	4	95	1	1	6.5	0.3
30	A	M703M	7	10	90	1	0	6.7	0.7
30	B	M615M	11	31	69	<1	0	7.6	3.4
30	B	M723M	6	16	84	<1	1	4.9	0.9
30	B	M643M	13	22	78	1	0	10.0	2.8
30	C	M731M	13	11	89	<1	0	11.7	1.5
30	C	M686M	9	15	84	2	1	7.2	1.4
30	C	M651M	11	31	68	<1	0	7.5	3.4
30	D	M752M	6	50	48	<1	1	2.9	3.0
30	D	M748M	9	46	53	1	0	4.6	4.0
30	D	M679M	10	43	57	2	0	5.5	4.1
30	E	M728M	9	48	49	<1	0	4.5	4.4
30	E	M727M	11	47	53	2	1	6.0	5.4
30	E	M613M	8	49	50	1	1	3.8	3.7
30	F	M642M	10	57	43	1	1	4.3	5.7
30	F	M602M	10	48	50	<1	0	4.9	4.7
30	F	M618M	12	37	62	<1	0	7.2	4.3
30	G	M627M	9	39	58	1	1	5.1	3.4
30	H	M746M	10	33	67	1	1	6.8	3.4
30	H	M676M	7	42	53	1	1	3.8	3.0
30	H	M709M	7	46	52	<1	<1	3.8	3.4
30	I	M729M	7	40	58	1	1	4.3	3.0
30	I	M740M	10	68	32	<1	0	3.1	6.5
30	I	M755M	8	35	64	1	0	5.1	2.8
30	J	M730M	14	56	43	<1	1	6.2	8.1
30	J	M660M	7	32	64	1	0	4.6	2.3

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
				DOSE = LD_{60} INHIBITOR = 3AB REPLICATE = 1					
30	J	M607M	6	43	55	<1	0	3.4	2.7
30	K	M734M	5	15	82	1	1	4.1	0.8
30	K	M754M	5	49	50	1	0	2.4	2.4
30	K	M733M	4	23	75	<1	0	2.9	0.9
30	K	M744M	16	51	48	<1	0	7.8	8.3
30	K	M713M	7	29	68	<1	0	4.8	2.0

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = 3AB REPLICATE = 2									
1	D	M877M	3	36	62	<1	1	1.7	1.0
1	D	M854M	2	79	21	<1	0	0.5	1.7
1	E	M883M	4	48	50	<1	1	1.8	1.7
1	E	M864M	2	83	17	1	1	0.4	2.0
1	F	M910M	3	80	19	1	0	0.5	2.1
1	F	M834M	4	86	11	1	0	0.4	3.3
1	G	M836M	3	94	6	<1	1	0.2	2.4
1	G	M841M	5	90	9	2	2	0.5	4.5
1	H	M844M	3	64	36	1	1	1.2	2.2
1	H	M848M	3	80	20	<1	<1	0.6	2.6
1	I	M929M	4	76	24	<1	0	0.9	2.7
1	I	M860M	2	78	22	1	1	0.4	1.2
1	J	M842M	4	71	26	1	0	1.1	3.0
1	J	M843M	3	82	18	1	0	0.5	2.5
1	K	M845M	5	42	58	<1	2	3.0	2.2
1	K	M893M	2	56	42	1	1	1.0	1.3
1	K	M805M	5	23	76	<1	0	3.6	1.1
1	K	M833M	4	42	57	<1	0	2.2	1.6
1	K	M856M	4	64	32	<1	0	1.2	2.4
1	K	M889M	6	70	30	1	0	1.9	4.5
2	D	M878M	1	52	47	1	.	0.3	0.3
2	D	M900M	9	56	43	1	11	3.7	4.8
2	E	M804M	2	51	49	<1	.	1.0	1.0
2	E	M922M	4	47	53	1	.	1.9	1.7
2	F	M882M	2	75	25	1	.	0.6	1.8
2	F	M923M	2	93	7	1	.	0.1	1.5
2	G	M896M	2	87	13	2	.	0.2	1.6
2	G	M817M	2	79	21	<1	.	0.3	1.3
2	H	M807M	2	75	25	<1	.	0.5	1.5
2	H	M907M	3	41	59	1	.	1.5	1.1
2	I	M803M	1	54	46	1	7	0.6	0.8
2	I	M897M	2	85	15	<1	.	0.4	2.0
2	J	M871M	4	77	23	<1	.	0.9	2.9
2	J	M931M	6	89	11	1	.	0.6	5.2
2	K	M917M	3	92	8	2	0	0.2	2.8
2	K	M851M	1	89	11	<1	.	0.1	1.1
2	K	M812M	3	58	42	<1	.	1.4	2.0
2	K	M852M	2	32	68	<1	.	1.6	0.8
2	K	M916M	3	80	19	<1	.	0.5	2.2

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
		DOSE = LD_{60} INHIBITOR = 3AB REPLICATE = 2							
2	K	M905M	1	65	35	1	.	0.4	0.8
3	D	M862M	2	38	62	1	.	1.4	0.8
3	D	M835M	0	18	82	0	.	0.2	0.0
3	E	M874M	1	19	81	1	.	0.5	0.1
3	E	M857M	1	4	96	1	.	0.6	0.0
3	F	M850M	0	.	.	<1	.	.	.
3	F	M895M	1	3	97	<1	.	0.6	0.0
3	G	M876M	1	5	95	0	.	0.8	0.0
3	G	M901M	0	32	68	<1	.	0.3	0.1
3	H	M927M	0	9	91	<1	.	0.2	0.0
3	H	M859M	1	1	99	<1	.	1.0	0.0
3	I	M908M	2	88	12	<1	.	0.2	1.4
3	I	M918M	6	15	81	<1	0	4.9	0.9
3	J	M837M	1	48	52	<1	.	0.5	0.5
3	J	M924M	0	45	55	0	.	0.1	0.1
3	K	M887M	1	7	93	<1	.	0.9	0.1
3	K	M906M	2	22	78	1	.	1.4	0.4
3	K	M823M	1	45	55	<1	.	0.6	0.5
3	K	M820M	1	17	83	0	.	0.5	0.1
3	K	M849M	1	13	87	<1	.	0.5	0.1
3	K	M891M	2	22	78	1	.	1.2	0.4
4	D	M827M	1	9	91	<1	.	0.5	0.1
4	D	M898M	0	.	.	<1	.	.	.
4	E	M879M	0	4	95	<1	.	0.4	0.0
4	E	M832M	1	5	95	0	.	0.8	0.0
4	F	M810M	1	2	98	<1	.	1.2	0.0
4	F	M920M	1	3	97	<1	.	1.4	0.0
4	G	M911M	1	3	97	1	.	0.8	0.0
4	G	M930M	1	2	98	<1	.	1.4	0.0
4	H	M892M	0	4	96	0	.	0.4	0.0
4	H	M844M	1	2	98	<1	.	0.6	0.0
4	I	M821M	1	7	93	1	.	1.1	0.1
4	I	M840M	3	0	100	1	0	3.0	0.0
4	J	M894M	0	9	91	0	.	0.2	0.0
4	J	M853M	2	6	94	<1	.	1.7	0.1
4	K	M846M	1	12	87	0	.	0.7	0.1
4	K	M825M	0	0	100	<1	.	0.4	0.0
4	K	M824M	0	3	97	1	.	0.4	0.0
4	K	M919M	.	8	92	1	.	.	.

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = 3AB REPLICATE = 2									
4	K	M913M	.	7	93	<1	.	.	.
4	K	M888M	0	5	95	1	.	0.4	0.0
5	D	M861M	1	3	97	1	.	0.8	0.0
5	D	M827M	2	5	95	<1	2	1.5	0.1
5	E	M922M	2	1	99	1	0	1.6	0.0
5	E	M857M	1	3	97	<1	.	0.6	0.0
5	F	M810M	1	1	99	<1	.	1.2	0.0
5	F	M920M	0	3	97	<1	.	0.4	0.0
5	G	M911M	1	5	95	1	.	1.1	0.1
5	G	M930M	1	0	100	<1	.	1.4	0.0
5	H	M844M	1	4	96	1	.	0.6	0.0
5	H	M907M	1	0	100	<1	0	0.8	0.0
5	I	M918M	8	19	80	<1	1	6.1	1.4
5	I	M821M	1	11	89	<1	0	0.9	0.1
5	J	M842M	2	3	97	<1	.	1.6	0.0
5	J	M853M	1	5	95	<1	.	1.1	0.1
5	K	M884M	0	9	91	<1	.	0.4	0.0
5	K	M893M	1	2	98	<1	1	0.8	0.0
5	K	M912M	0	4	96	<1	.	0.2	0.0
5	K	M805M	2	1	99	<1	1	1.8	0.0
5	K	M856M	1	0	100	<1	.	1.0	0.0
5	K	M889M	0	4	96	1	.	0.4	0.0
30	D	M877M	8	40	59	1	1	4.6	3.1
30	D	M878M	7	54	46	<1	<1	3.4	4.0
30	D	M900M	6	16	80	1	<1	4.8	1.0
30	E	M922M	10	34	65	<1	0	6.5	3.4
30	E	M857M	9	39	61	1	1	5.2	3.4
30	E	M879M	11	40	58	1	<1	6.1	4.2
30	F	M810M	9	31	68	1	0	5.8	2.7
30	G	M911M	6	27	70	<1	1	4.2	1.6
30	G	M930M	8	31	69	1	1	5.8	2.6
30	H	M844M	19	57	43	<1	1	8.1	10.7
30	H	M907M	7	31	67	1	1	4.4	2.0
30	H	M892M	5	32	65	<1	0	3.0	1.5
30	I	M918M	8	18	81	<1	2	6.2	1.4
30	I	M821M	4	24	75	1	0	3.3	1.1
30	I	M840M	10	23	74	1	0	7.1	2.2
30	J	M842M	9	56	44	1	1	3.9	4.9
30	J	M853M	10	29	69	<1	<1	6.6	2.8

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = 3AB REPLICATE = 2									
30	K	M893M	10	49	51	<1	0	4.9	4.7
30	K	M906M	9	10	87	<1	0	8.0	0.9
30	K	M884M	9	36	64	1	0	5.6	3.2
30	K	M805M	8	12	85	1	1	6.6	0.9
30	K	M812M	8	38	59	<1	0	4.6	3.0
30	K	M852M	7	35	63	<1	0	4.3	2.4
30	K	M856M	7	41	58	<1	<1	3.9	2.8
30	K	M889M	8	43	54	<1	1	4.4	3.5

TABLE 3.16.
(Continued)

DOSE = LD_{60} INHIBITOR = NA REPLICATE = I

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
1	A	M153M	5	11	87	<1	<1	4.7	0.6
1	A	M103M	8	16	84	<1	0	6.9	1.3
1	B	M89M	6	9	90	1	<1	5.4	0.5
1	B	M162M	8	12	88	<1	0	7.4	1.0
1	C	M200M	6	26	72	<1	1	4.3	1.6
1	C	M133M	11	11	85	<1	0	9.0	1.2
1	D	M65M	7	77	19	0	0	1.3	5.4
1	D	M142M	4	63	35	<1	2	1.5	2.8
1	E	M117M	6	25	72	1	5	4.5	1.6
1	E	M110M	3	60	39	1	2	1.2	1.9
1	F	M178M	3	39	59	<1	2	1.9	1.2
1	F	M150M	3	44	56	<1	9	1.9	1.5
1	G	M195M	5	27	73	1	6	3.8	1.4
1	G	M62M	9	100	0	<1	2	0.0	9.2
1	H	M60M	3	39	61	<1	1	2.0	1.2
1	H	M130M	6	33	67	2	3	4.0	2.0
1	I	M82M	6	93	6	1	0	0.3	5.4
1	I	M127M	5	31	69	1	2	3.5	1.6
1	J	M91M	3	63	36	<1	1	1.2	2.0
1	J	M96M	3	66	34	<1	2	1.2	2.2
1	K	M107M	6	91	9	<1	0	0.5	5.3
1	K	M121M	3	39	59	<1	1	2.0	1.3
1	K	M183M	3	67	33	<1	0	0.9	1.7
1	K	M174M	3	68	32	<1	2	0.8	1.8
1	K	M160M	4	49	50	<1	2	1.9	1.9
1	K	M154M	3	50	50	2	3	1.6	1.6
2	A	M90M	8	16	82	1	0	6.6	1.3
2	A	M78M	8	20	78	<1	0	6.1	1.6
2	B	M193M	12	11	87	1	0	10.8	1.4
2	B	M79M	5	16	82	<1	0	4.3	0.8
2	C	M149M	10	27	73	<1	0	7.4	2.8
2	C	M189M	10	26	71	<1	0	7.2	2.7
2	D	M63M	7	13	87	<1	.	6.1	0.9
2	D	M144M	4	66	34	<1	.	1.4	2.6
2	E	M131M	3	17	83	<1	.	2.5	0.5
2	E	M158M	4	51	49	1	.	1.9	1.9
2	F	M108M	3	51	49	1	.	1.7	1.7
2	F	M111M	2	40	59	1	.	1.4	1.0
2	G	M124M	2	66	34	1	.	0.8	1.6

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = NA REPLICATE = 1									
2	G	M148M	5	76	24	<1	.	1.1	3.5
2	H	M132M	3	77	23	<1	.	0.7	2.5
2	H	M64M	3	60	40	<1	.	1.4	2.0
2	I	M61M	4	35	65	1	.	2.3	1.3
2	I	M197M	2	61	39	1	.	0.9	1.3
2	J	M161M	3	67	33	<1	.	0.9	1.9
2	J	M67M	4	88	12	<1	.	0.5	3.9
2	K	M156M	3	68	32	2	.	1.0	2.2
2	K	M159M	4	86	14	<1	.	0.5	3.3
2	K	M167M	5	79	21	2	.	1.1	4.1
2	K	M155M	5	70	30	<1	.	1.4	3.2
2	K	M95M	3	66	34	1	.	1.2	2.2
2	K	M50M	5	22	77	1	.	3.9	1.1
3	A	M120M	9	15	84	1	2	7.4	1.3
3	A	M169M	9	5	94	1	3	8.3	0.4
3	B	M175M	7	22	76	<1	0	5.3	1.5
3	B	M186M	10	18	80	<1	1	8.0	1.8
3	C	M141M	9	11	89	<1	1	7.8	1.0
3	C	M172M	7	15	80	1	0	5.6	1.1
3	D	M123M	1	11	89	<1	.	0.9	0.1
3	D	M166M	0	13	87	2	.	0.3	0.1
3	E	M182M	1	18	82	1	.	0.5	0.1
3	E	M54M	1	7	93	1	.	1.1	0.1
3	F	M105M	2	17	83	<1	.	1.8	0.4
3	F	M66M	2	8	92	<1	.	2.0	0.2
3	G	M112M	1	3	97	1	.	0.6	0.0
3	G	M73M	0	11	89	<1	.	0.2	0.0
3	H	M102M	1	7	93	<1	.	1.3	0.1
3	H	M198M	0	6	93	<1	.	0.4	0.0
3	I	M53M	2	18	82	1	.	1.3	0.3
3	I	M191M	1	17	83	<1	.	0.8	0.2
3	J	M75M	0	13	87	1	.	0.2	0.0
3	J	M92M	3	22	78	1	.	2.3	0.7
3	K	M113M	1	12	88	<1	.	0.5	0.1
3	K	M84M	0	9	91	1	.	0.4	0.0
3	K	M165M	3	18	82	<1	.	2.8	0.6
3	K	M97M	0	27	73	1	.	0.3	0.1
3	K	M181M	2	21	79	<1	.	1.6	0.4
3	K	M106	1	32	67	1	.	0.5	0.3

TABLE 3.16.
(Continued)

DOSE = LD_{60} INHIBITOR = NA REPLICATE = 1

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
4	A	M135M	8	5	94	1	1	7.5	0.4
4	A	M81M	11	5	94	1	2	10.3	0.6
4	B	M70M	13	24	75	1	1	9.5	3.0
4	B	M58M	15	11	89	<1	0	13.4	1.7
4	C	M196M	14	14	85	1	1	12.2	2.0
4	C	M77M	6	15	84	1	0	5.2	0.9
4	D	M119M	1	3	97	<1	.	1.0	0.0
4	D	M86M	1	7	92	<1	.	0.7	0.1
4	E	M126M	0	32	68	<1	.	-0.1	-0.0
4	E	M177M	2	6	94	1	.	1.5	0.1
4	F	M157M	0	7	93	<1	.	0.2	0.0
4	F	M173M	1	3	97	2	2	1.0	0.0
4	G	M98M	0	9	91	<1	.	0.4	0.0
4	G	M88M	2	8	91	<1	.	1.5	0.1
4	H	M55M	0	3	97	1	.	0.2	0.0
4	H	M139M	1	4	96	2	.	0.6	0.0
4	I	M170M	0	6	94	1	.	0.4	0.0
4	I	M151M	1	4	96	<1	.	0.8	0.0
4	J	M140M	1	5	95	1	.	0.8	0.0
4	J	M176M	1	6	94	<1	.	0.8	0.0
4	K	M109M	1	1	99	<1	.	1.4	0.0
4	K	M171M	1	3	97	<1	.	1.4	0.0
4	K	M187M	1	0	100	<1	.	0.6	0.0
4	K	M146M	1	2	98	2	.	0.8	0.0
4	K	M192M	1	5	95	<1	.	0.6	0.0
4	K	M59M	2	1	99	1	.	1.6	0.0
5	A	M190M	8	19	76	1	0	5.8	1.4
5	A	M164M	13	20	79	1	0	10.4	2.6
5	B	M137M	11	16	82	<1	1	9.3	1.8
5	B	M68M	7	12	86	<1	2	6.4	0.9
5	C	M163M	12	17	82	1	0	10.0	2.1
5	C	M74M	11	18	82	<1	0	9.0	2.0
5	D	M85M	2	1	99	1	.	1.6	0.0
5	D	M142M	0	.	.	<1	.	.	.
5	E	M188M	2	3	97	<1	.	1.7	0.1
5	E	M117M	2	3	97	<1	0	1.9	0.1
5	F	M180M	1	4	96	<1	0	1.0	0.0
5	F	M173M	1	3	97	1	1	1.4	0.0
5	G	M195M	7	11	89	1	1	5.9	0.7

TABLE 3.16.
(Continued)

DOSE = LD_{60} INHIBITOR = NA REPLICATE = 1

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
5	G	M148M	1	5	95	<1	0	0.6	0.0
5	H	M57M	1	9	91	<1	.	0.7	0.1
5	H	M100M	1	0	100	<1	0	1.4	0.0
5	I	M136M	0	5	95	<1	.	0.4	0.0
5	I	M53M	2	8	92	1	0	1.5	0.1
5	J	M92M	2	9	90	<1	.	1.4	0.1
5	J	M75M	0	6	94	<1	.	0.4	0.0
5	K	M121M	.	.	.	.	.	.	.
5	K	M185M	0	2	98	1	.	0.4	0.0
5	K	M152M	1	1	99	<1	.	0.8	0.0
5	K	M69M	0	.	.	<1	.	.	.
5	K	M56M	2	4	96	<1	.	1.9	0.1
5	K	M50M	3	3	96	1	0	3.1	0.1
30	A	M153M	7	15	85	1	0	5.8	1.0
30	A	M103M	10	13	86	1	0	8.9	1.4
30	A	M090M	8	25	74	1	1	6.1	2.1
30	B	M089M	6	19	81	<1	0	5.0	1.2
30	B	M162M	11	24	76	<1	1	8.1	2.5
30	B	M193M	12	28	70	<1	0	8.3	3.3
30	C	M200M	6	13	87	<1	0	5.6	0.8
30	C	M133M	10	10	90	<1	1	9.4	1.0
30	C	M149M	9	24	73	1	0	6.3	2.1
30	D	M063M	11	22	76	1	0	8.2	2.4
30	D	M144M	11	47	50	<1	1	5.6	5.3
30	D	M123M	12	71	28	1	0	3.2	8.2
30	E	M117M	4	13	87	<1	2	3.3	0.5
30	E	M131M	6	16	82	<1	2	4.9	1.0
30	E	M158M	10	32	67	1	1	6.4	3.1
30	F	M150M	7	32	65	<1	1	4.6	2.2
30	F	M108M	15	53	46	<1	1	6.9	8.0
30	F	M111M	9	26	73	<1	0	6.3	2.2
30	G	M195M	13	24	75	1	0	9.5	3.0
30	G	M148M	11	42	56	<1	0	6.4	4.8
30	G	M112M	6	37	62	1	0	3.7	2.2
30	H	M064M	8	40	60	<1	0	5.0	3.4
30	H	M102M	4	35	64	1	0	2.8	1.5
30	H	M057M	8	32	68	<1	0	5.4	2.6
30	I	M127M	10	24	73	<1	<1	7.4	2.4
30	I	M061M	3	68	32	1	1	1.0	2.0

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
			DOSE = LD_{60} INHIBITOR = NA REPLICATE = 1						
30	J	M197M	6	20	80	<1	0	4.8	1.2
30	J	M091M	7	42	57	<1	1	4.2	3.1
30	J	M096M	10	32	67	<1	0	6.8	3.3
30	J	M067M	11	59	40	<1	1	4.2	6.3
30	K	M121M	10	40	57	<1	0	5.5	3.8
30	K	M109M	11	21	77	<1	0	8.8	2.4
30	K	M174M	11	60	39	1	0	4.4	6.8
30	K	M155M	9	53	47	1	1	4.3	4.9
30	K	M165M	9	35	65	1	0	6.0	3.2
30	K	M160M	12	31	67	<1	0	8.0	3.7
30	K	M154M	12	34	66	<1	0	7.8	4.0
30	K	M050M	10	25	69	1	0	6.9	2.5

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = NA REPLICATE = 2									
1	D	M650M	6	63	35	1	1	2.2	4.0
1	D	M694M	6	80	20	1	0	1.1	4.5
1	E	M695M	3	88	12	1	2	0.4	2.6
1	E	M692M	1	66	34	<1	2	0.4	0.8
1	F	M686M	3	48	51	<1	3	1.5	1.4
1	F	M631M	5	58	42	<1	1	2.2	3.0
1	G	M615M	2	84	16	<1	2	0.4	1.8
1	G	M616M	5	40	59	2	1	3.1	2.1
1	H	M628M	3	84	16	<1	0	0.4	2.2
1	H	M653M	3	57	43	<1	1	1.3	1.7
1	I	M599M	2	81	19	<1	0	0.3	1.3
1	I	M611M	3	90	10	<1	1	0.3	2.9
1	J	M622M	5	79	21	1	2	1.1	4.0
1	J	M669M	4	67	33	<1	0	1.2	2.4
1	K	M698M	5	92	8	1	0	0.4	5.0
1	K	M621M	4	80	19	<1	0	0.7	3.0
1	K	M645M	2	64	36	1	1	0.7	1.3
1	K	M688M	6	58	42	<1	3	2.6	3.6
1	K	M626M	4	86	14	<1	0	0.5	3.1
1	K	M658M	3	67	33	<1	2	1.0	2.0
2	D	M682M	3	54	46	<1	.	1.6	1.8
2	D	M625M	7	93	7	<1	.	0.5	6.3
2	E	M679M	2	65	35	<1	.	0.8	1.6
2	E	M641M	3	79	21	<1	.	0.6	2.4
2	F	M605M	2	72	28	1	.	0.6	1.6
2	F	M660M	5	79	21	<1	.	1.0	3.8
2	G	M592M	1	73	27	1	.	0.3	0.7
2	G	M634M	2	52	48	<1	.	0.9	0.9
2	H	M670M	4	79	21	1	.	0.8	2.8
2	H	M578M	2	92	8	1	.	0.2	2.2
2	I	M681M	4	38	61	1	.	2.4	1.5
2	I	M603M	1	72	27	1	.	0.4	1.0
2	J	M691M	3	59	41	<1	.	1.1	1.5
2	J	M635M	3	65	35	<1	.	1.0	1.8
2	K	M693M	2	72	26	<1	.	0.4	1.2
2	K	M604M	5	85	15	<1	.	0.7	3.9
2	K	M591M	3	87	13	1	.	0.3	2.3
2	K	M633M	3	61	39	<1	.	1.2	1.8
3	D	M696M	2	30	70	0	.	1.4	0.6

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
				DOSE = LD_{60} INHIBITOR = NA REPLICATE = 2					
3	D	M663M	0	38	62	2	.	0.2	0.2
3	E	M677M	0	9	91	1	.	0.4	0.0
3	E	M639M	2	38	62	1	.	1.4	0.8
3	F	M607M	0	19	81	<1	.	0.3	0.1
3	F	M585M	0	6	94	<1	.	0.4	0.0
3	G	M700M	0	28	72	1	.	0.1	0.1
3	G	M588M	2	21	79	1	.	1.7	0.5
3	H	M646M	1	54	46	<1	.	0.6	0.6
3	H	M648M	1	23	77	1	.	0.9	0.3
3	I	M675M	1	34	66	1	.	0.7	0.3
3	I	M659M	0	17	83	1	.	0.3	0.1
3	J	M668M	1	5	95	1	.	0.8	0.0
3	J	M684M	1	34	66	<1	.	0.5	0.3
3	K	M654M	0	3	97	<1	.	0.2	0.0
3	K	M661M	0	19	81	1	.	0.2	0.0
3	K	M636M	0	19	81	<1	.	0.3	0.1
3	K	M581M	0	23	77	1	.	0.3	0.1
3	K	M647M	0	18	82	2	.	0.3	0.1
3	K	M685M	1	17	33	<1	.	1.0	0.2
4	D	M613M	0	3	97	<1	.	0.4	0.0
4	D	M664M	0	2	98	<1	.	0.2	0.0
4	E	M662M	0	15	85	1	.	0.3	0.1
4	E	M687M	0	14	86	<1	.	0.3	0.1
4	F	M582M	0	7	93	<1	.	0.4	0.0
4	F	M609M	0	.	.	0	.	.	.
4	G	M651M	0	1	98	<1	.	0.4	0.0
4	G	M600M	0	2	98	<1	.	0.4	0.0
4	H	M580M	0	5	95	<1	.	0.2	0.0
4	H	M665M	0	2	98	1	.	0.4	0.0
4	I	M644M	0	3	97	<1	.	0.2	0.0
4	I	M614M	1	2	98	1	.	1.0	0.0
4	J	M629M	0	6	94	1	.	0.2	0.0
4	J	M667M	0	5	95	<1	.	0.2	0.0
4	K	M606M	0	4	96	<1	.	0.4	0.0
4	K	M577M	0	1	99	1	.	0.2	0.0
4	K	M620M	1	3	97	<1	.	0.8	0.0
4	K	M575M	0	0	100	<1	.	0.2	0.0
4	K	M680M	0	.	.	<1	.	.	.
4	K	M637M	0	2	98	<1	.	0.2	0.0

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = NA REPLICATE = 2									
5	D	M617M	1	0	100	1	.	0.6	0.0
5	D	M682M	1	9	91	1	0	0.5	0.1
5	E	M641M	0	3	97	1	.	0.2	0.0
5	E	M677M	0	7	93	<1	0	0.2	0.0
5	F	M631M	1	12	88	1	0	0.9	0.1
5	F	M582M	0	0	100	<1	.	0.4	0.0
5	G	M616M	2	0	100	1	.	2.4	0.0
5	G	M588M	1	5	95	<1	.	1.0	0.1
5	H	M580M	0	4	96	<1	.	0.4	0.0
5	H	M646M	0	6	94	<1	.	0.4	0.0
5	I	M623M	0	8	92	1	.	0.4	0.0
5	I	M681M	1	1	99	<1	1	0.8	0.0
5	J	M583M	0	7	93	1	.	0.2	0.0
5	J	M622M	1	6	94	<1	0	0.9	0.1
5	K	M576M	1	7	93	1	.	0.6	0.0
5	K	M606M	0	4	96	1	.	0.4	0.0
5	K	M688M	2	3	97	2	1	1.6	0.0
5	K	M620M	1	3	96	1	.	0.8	0.0
5	K	M637M	0	6	94	<1	.	0.4	0.0
5	K	M591M	.	9	91	<1	.	.	.
30	D	M694M	14	48	52	<1	0	7.1	6.5
30	D	M682M	11	61	38	1	0	4.3	7.0
30	D	M696M	8	24	75	<1	0	6.2	2.0
30	E	M641M	9	54	45	<1	0	4.0	4.8
30	E	M677M	8	56	43	1	0	3.5	4.6
30	E	M639M	10	42	56	<1	0	5.8	4.4
30	F	M631M	18	58	40	<1	1	7.3	10.6
30	F	M605M	12	63	35	1	0	4.3	7.7
30	F	M660M	5	50	46	1	2	2.4	2.6
30	G	M616M	12	40	58	1	<1	7.2	5.0
30	G	M588M	8	42	58	<1	0	4.8	3.4
30	G	M600M	9	53	46	1	1	4.3	5.0
30	H	M646M	9	54	46	1	0	4.3	5.1
30	H	M580M	8	49	50	1	0	3.8	3.7
30	H	M653M	11	44	52	<1	0	5.9	5.0
30	I	M623M	8	52	48	<1	2	4.0	4.4
30	I	M644M	7	62	35	<1	0	2.5	4.3
30	I	M681M	13	62	37	<1	1	4.8	8.1
30	J	M622M	10	66	34	1	0	3.3	6.3

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = NA REPLICATE = 2									
30	J	M635M	8	75	25	.1	0	2.0	5.9
30	J	M668M	13	62	36	<1	0	4.5	7.8
30	K	M606M	11	64	35	<1	0	3.8	6.9
30	K	M576M	12	49	49	1	1	5.8	5.8
30	K	M688M	12	60	39	<1	1	4.6	7.1
30	K	M620M	11	56	44	<1	2	4.8	6.0
30	K	M581M	18	55	45	2	1	8.2	10.0
30	K	M685M	10	59	39	1	1	3.8	5.8

TABLE 3.16.
(Continued)

DOSE = LD$_{60}$ INHIBITOR = NIC REPLICATE = 1

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
1	A	M1138	5	19	81	<1	0	3.9	0.9
1	A	M0479	14	26	69	1	0	9.3	3.5
1	B	M1172	10	28	68	1	0	7.0	2.9
1	B	M1146	11	22	75	<1	0	8.0	2.3
1	C	M1187	8	36	62	<1	0	5.0	2.9
1	C	M1140	6	13	86	1	2	5.0	0.8
1	D	M0455	6	65	35	1	1	2.0	3.7
1	D	M0444	7	10	88	1	0	6.2	0.7
1	E	M1169	4	78	22	<1	2	0.9	3.2
1	E	M0480	5	68	30	<1	5	1.4	3.1
1	F	M0451	6	78	22	1	1	1.3	4.5
1	F	M1163	6	98	2	<1	1	0.1	6.3
1	G	M1197	4	73	27	<1	2	1.2	3.2
1	G	M1141	3	72	25	<1	1	0.9	2.4
1	H	M0422	7	91	9	<1	0	0.6	6.5
1	H	M0408	3	53	47	1	2	1.6	1.7
1	I	M0499	5	49	50	1	3	2.3	2.3
1	I	M0469	7	72	28	<1	<1	1.8	4.8
1	J	M0491	4	59	40	<1	5	1.8	2.6
1	J	M0432	6	89	11	1	1	0.7	5.4
1	K	M0497	7	84	16	1	1	1.2	6.1
1	K	M0440	4	70	30	<1	1	1.3	3.0
2	A	M1176	.	32	65	<1	2	.	.
2	A	M0477	9	22	78	1	2	7.2	2.0
2	B	M0438	14	17	82	1	0	11.6	2.4
2	B	M0454	10	25	74	1	2	7.3	2.5
2	C	M0490	10	14	85	<1	0	8.7	1.4
2	C	M1196	8	17	82	<1	1	6.2	1.3
2	D	M1193	4	58	42	1	.	1.8	2.4
2	D	M0482	4	34	66	1	84	2.6	1.4
2	E	M1128	4	75	25	1	70	0.9	2.7
2	E	M1105	3	84	14	1	.	0.5	2.9
2	F	M0456	4	77	23	<1	.	1.0	3.2
2	F	M0466	1	93	7	<1	16	0.1	1.3
2	G	M1109	3	49	51	1	.	1.3	1.3
2	G	M0494	.	81	19	1	.	.	.
2	H	M1132	.	78	22	1	.	.	.
2	H	M1161	3	64	36	<1	.	1.0	1.8
2	I	M1143	3	55	45	1	.	1.2	1.4

TABLE 3.16.
(Continued)

DOSE = LD_{60} INHIBITOR = NIC REPLICATE = 1

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
2	I	M1158	.	60	40	1	.	.	.
2	J	M0474	.	81	19	1	.	.	.
2	J	M0478	4	83	17	1	.	0.7	3.7
2	K	M0427	3	83	17	<1	.	0.5	2.5
2	K	M0423	3	62	38	1	.	1.3	2.1
3	A	M0483	8	28	70	1	0	5.5	2.2
3	A	M1104	11	20	78	1	1	8.6	2.2
3	B	M1164	18	35	62	<1	1	10.9	6.2
3	B	M1111	12	26	71	<1	0	8.4	3.1
3	C	M0428	11	26	71	<1	1	7.7	2.8
3	C	M1194	7	26	73	1	0	5.0	1.8
3	D	M0436	1	28	72	<1	.	0.6	0.2
3	D	M1191	1	55	45	1	.	0.4	0.4
3	E	M0442	1	73	27	1	.	0.2	0.4
3	E	M0489	0	25	75	1	.	0.3	0.1
3	F	M0481	1	14	86	<1	.	0.5	0.1
3	F	M1135	1	13	87	1	.	0.7	0.1
3	G	M0458	2	79	21	<1	.	0.5	1.7
3	G	M0430	1	7	93	1	.	0.7	0.1
3	H	M1129	1	18	82	1	.	0.7	0.1
3	H	M1106	1	16	84	1	.	0.5	0.1
3	I	M0425	8	33	67	1	.	5.2	2.6
3	I	M1177	1	8	92	<1	.	0.7	0.1
3	J	M0415	1	75	25	<1	.	0.3	0.8
3	J	M0446	1	30	70	1	.	0.8	0.4
3	K	M0410	1	26	74	<1	.	0.9	0.3
3	K	M0420	0	8	92	<1	.	0.4	0.0
4	A	M1147	7	21	79	1	1	5.8	1.6
4	A	M0416	10	34	65	<1	1	6.8	3.5
4	B	M1126	15	46	53	1	0	7.8	6.8
4	B	M1139	10	29	70	<1	0	6.9	2.8
4	C	M0485	11	21	74	1	0	8.1	2.3
4	C	M0468	9	7	91	<1	0	8.6	0.7
4	D	M0455	0	12	88	<1	.	0.4	0.0
4	D	M0444	9	22	78	1	2	7.3	2.1
4	E	M0463	3	13	87	1	.	2.3	0.3
4	E	M0462	0	28	72	1	.	0.1	0.1
4	F	M1186	1	11	89	2	.	1.1	0.1
4	F	M0402	0	16	84	2	.	0.2	0.0

TABLE 3.16.
(Continued)

DOSE = LD_{60} INHIBITOR = NIC REPLICATE = 1

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
4	G	M1197	0	10	90	1	.	0.2	0.0
4	G	M1109	1	8	92	2	.	0.7	0.1
4	H	M0412	1	3	97	3	.	1.2	0.0
4	H	M0450	0	12	88	1	.	0.4	0.0
4	I	M1156	0	17	83	2	.	0.3	0.1
4	I	M0409	1	14	86	1	.	0.5	0.1
4	J	M1170	2	15	85	1	.	1.5	0.3
4	J	M1171	0	9	91	2	.	0.4	0.0
4	K	M0431	2	4	96	1	.	1.5	0.1
4	K	M0433	1	12	88	1	.	0.5	0.1
5	A	M0467	13	36	64	1	0	8.1	4.5
5	A	M1103	7	18	81	1	0	5.8	1.3
5	B	M0449	5	18	76	<1	0	4.1	1.0
5	B	M0460	15	23	76	<1	0	11.2	3.4
5	C	M0472	11	28	71	1	2	7.8	3.1
5	C	M1112	9	29	70	2	1	6.4	2.7
5	D	M1193	1	5	95	<1	0	0.6	0.0
5	D	M1191	0	8	92	1	0	0.4	0.0
5	E	M0463	2	6	94	<1	.	2.3	0.1
5	E	M0480	1	7	93	2	1	0.9	0.1
5	F	M0481	0	7	93	1	.	0.4	0.0
5	G	M1109	0	3	97	2	1	0.4	0.0
5	G	M0430	1	4	96	<1	.	0.8	0.0
5	H	M0406	0	4	96	1	.	0.4	0.0
5	H	M1195	2	23	77	1	2	1.7	0.5
5	I	M0484	1	7	92	<1	.	0.6	0.0
5	I	M0425	4	23	74	2	2	3.3	1.0
5	J	M1181	1	0	99	7	0	1.0	0.0
5	J	M0491	1	4	96	1	2	0.6	0.0
5	K	M1131	1	3	97	1	.	0.8	0.0
5	K	M0423	1	2	98	3	.	0.6	0.0
30	A	M1138	7	38	62	1	1	4.3	2.7
30	A	M0479	12	25	72	1	1	8.6	3.0
30	A	M1176	11	12	86	2	0	9.1	1.3
30	B	M1172	9	20	77	<1	1	7.1	1.8
30	B	M1146	9	13	84	<1	2	7.7	1.2
30	B	M0438	7	18	81	1	1	5.8	1.3
30	C	M1187	9	18	79	<1	0	6.8	1.5
30	C	M1140	6	18	81	<1	0	5.0	1.1

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
		DOSE = LD_{60} INHIBITOR = NIC REPLICATE = 1							
30	C	M0490	10	13	86	<1	1	8.9	1.4
30	D	M0444	12	22	76	<1	0	8.8	2.6
30	D	M1193	8	44	55	2	1	4.2	3.3
30	D	M1191	11	63	36	<1	0	3.8	6.7
30	E	M0480	8	37	63	<1	1	5.3	3.1
30	E	M0463	11	26	71	<1	0	8.1	3.0
30	F	M0481	10	47	47	1	0	4.6	4.6
30	H	M0450	12	54	44	<1	<1	5.3	6.5
30	H	M0406	8	40	55	1	1	4.6	3.4
30	H	M1195	10	27	67	<1	1	6.8	2.8
30	I	M0469	8	55	44	2	1	3.6	4.5
30	I	M0425	13	24	75	<1	0	9.9	3.2
30	I	M0409	10	53	45	1	1	4.7	5.5
30	J	M0491	6	43	56	1	1	3.5	2.7
30	J	M0432	6	49	48	1	0	2.9	2.9
30	J	M1170	9	33	67	1	<1	6.2	3.0
30	K	M0431	6	20	77	<1	2	4.5	1.2
30	K	M1131	8	38	62	1	0	5.0	3.0

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = NIC REPLICATE = 2									
1	D	M0501	2	67	33	<1	.	0.6	1.2
1	D	M0421	2	87	13	<1	2	0.3	1.7
1	E	M0450	2	29	69	1	3	1.5	0.6
1	E	M0495	2	69	28	<1	8	0.4	1.1
1	F	M0458	2	59	40	1	3	0.7	1.1
1	G	M0403	4	93	7	1	3	0.3	3.7
1	G	M0425	1	74	26	1	4	0.3	0.9
1	H	M0469	3	59	39	<1	4	1.0	1.5
1	I	M0414	4	96	3	<1	1	0.1	3.6
1	I	M0462	3	50	48	<1	3	1.3	1.4
1	J	M0505	3	79	21	1	2	0.7	2.7
1	J	M0473	4	71	26	1	5	1.0	2.8
1	K	M0434	3	77	22	1	1	0.7	2.3
2	D	M0325	4	87	13	1	.	0.5	3.1
2	D	M0494	2	64	36	1	.	0.8	1.4
2	E	M0411	2	85	15	1	.	0.3	1.9
2	F	M0503	1	74	26	2	.	0.3	0.9
2	F	M0415	3	81	19	3	.	0.5	2.3
2	G	M0416	3	88	12	1	.	0.4	2.8
2	G	M0423	2	69	30	<1	.	0.5	1.1
2	H	M0446	3	81	19	1	.	0.6	2.4
2	H	M0456	2	66	34	<1	.	0.7	1.5
2	J	M0402	3	92	8	1	5	0.2	2.8
2	J	M0457	2	82	18	1	.	0.4	2.0
2	K	M0443	2	71	29	1		0.6	1.4
2	K	M0437	1	78	22	<1	.	0.2	0.8
3	D	M0493	1	44	56	1	.	0.6	0.4
3	D	M0490	1	40	60	1	.	0.7	0.5
3	E	M0463	1	15	85	<1	.	0.9	0.2
3	E	M0417	0	5	94	<1	.	0.4	0.0
3	F	M0413	0	3	97	<1	.	.	.
3	F	M0454	0	50	50	1	.	0.1	0.1
3	G	M0484	0	14	86	2	.	0.2	0.0
3	G	M0439	1	6	94	1	.	0.6	0.0
3	H	M0491	0	78	22	1	.	0.1	0.3
3	H	M0465	1	22	77	2	.	0.9	0.3
3	I	M0498	0	8	92	1	.	0.4	0.0
3	I	M0441	1	25	75	<1	.	0.6	0.2
3	J	M0476	1	13	87	1	.	1.0	0.2

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = NIC REPLICATE = 2									
3	J	M0419	0	5	95	<1	.	0.2	0.0
3	K	M0453	1	12	88	<1	.	0.5	0.1
3	K	M0431	1	23	77	1	.	0.6	0.2
4	D	M0426	1	7	93	<1	.	0.7	0.1
4	D	M0481	1	2	98	1	.	0.6	0.0
4	E	M0455	1	8	92	<1	.	0.7	0.1
4	E	M0516	.	9	91	1	.	.	.
4	F	M0466	0	18	82	1	.	0.2	0.0
4	F	M0503	0	16	84	1	.	0.2	0.0
4	G	M0475	0	0	100	1	.	-0.2	0.0
4	G	M0448	2	4	96	2	.	1.5	0.1
4	H	M0440	1	8	92	<1	.	0.6	0.0
4	H	M0486	0	14	86	1	.	0.3	0.1
4	I	M0471	0	11	89	1	.	0.2	0.0
4	I	M0444	0	22	78	<1	.	0.2	0.0
4	J	M0461	1	6	94	1	.	0.6	0.0
4	J	M0488	1	18	82	<1	.	0.5	0.1
4	K	M0429	0	5	95	1	.	0.4	0.0
4	K	M0443	1	22	78	1	.	0.5	0.1
5	D	M0405	2	1	99	1	0	1.8	0.0
5	E	M0499	1	6	94	<1	1	0.8	0.0
5	E	M0450	1	3	97	<1	1	0.6	0.0
5	G	M0440	0	2	97	1	.	0.4	0.0
5	H	M0469	0	10	90	1	2	0.4	0.0
5	H	M0446	.	9	90	1	.	.	.
5	I	M0414	0	5	95	<1	.	0.2	0.0
5	J	M0505	1	2	98	1	.	0.6	0.0
5	J	M0473	1	8	92	<1	.	0.7	0.1
30	D	M408M	5	28	70	1	<1	3.8	1.5
30	D	M493M	14	46	52	<1	0	7.5	6.6
30	D	M490M	11	61	39	<1	0	4.4	7.0
30	E	M450M	6	24	74	1	0	4.1	1.3
30	E	M463M	10	57	42	1	1	4.1	5.6
30	E	M417M	9	67	33	<1	1	3.1	6.3
30	F	M503M	10	63	37	1	1	3.7	6.3
30	F	M415M	15	60	39	<1	2	5.9	9.0
30	G	M423M	8	59	41	<1	0	3.4	4.8
30	G	M440M	11	60	39	<1	1	4.4	6.8
30	H	M469M	5	58	40	<1	2	2.1	3.0

TABLE 3.16.
(Continued)

DAY	GROUP	ANIMAL	WBC	SEG	LYMPH	MICNORM	MICPOLY	ABSLYMPH	ABSSEG
DOSE = LD_{60} INHIBITOR = NIC REPLICATE = 2									
30	H	M446M	9	64	36	<1	2	3.4	6.0
30	H	M456M	8	21	78	<1	0	6.4	1.7
30	I	M414M	8	68	30	1	0	2.3	5.2
30	I	M462M	8	53	44	1	0	3.5	4.2
30	I	M498M	7	54	46	<1	0	3.4	4.0
30	J	M505M	8	44	55	1	0	4.6	3.7
30	J	M473M	9	34	65	1	<1	5.6	2.9
30	J	M476M	7	44	56	<1	1	4.0	3.2
30	K	M429M	12	47	51	<1	1	6.1	5.6
30	K	M431M	6	37	59	<1	0	3.7	2.3

WBC = White Blood Cells (thousands per $\mu\ell$)
ABSSEG = Absolute Segmented Neutrophils (thousands per $\mu\ell$)
ABSLYMPH = Absolute Lymphocytes (thousands per $\mu\ell$)
MICNORM = Micronucleated Cells/500 Normochromatic Erythrocytes
MICPOLY = Micronucleated Cells/500 Polychromatic Erythrocytes
SEG = Segmented Neutrophils (percent of total WBC)
LYMPH = Lymphocytes (percent of total WBC)
3AB = 3-Aminobenzamide
NIC = Nicotinamide
NA = Nicotinic Acid

TABLE 3.17. SUMMARY OF HEMATOLOGY VARIABLES FOR NO-HD GROUPS DOSED UNDER MREF PROTOCOL 19 INHIBITOR STUDIES

		HD DOSE = LD_{30}								
			WBC			ABSSEG			ABSLYMPH	
GROUP	DAY	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
B	1	6	6.30	2.14	6	1.17	0.94	6	4.99	1.49
	2	6	8.77	3.36	6	2.06	1.34	6	6.51	2.40
	3	5	7.84	1.76	5	1.61	1.21	5	6.15	1.25
	4	5	8.28	0.95	5	1.01	0.63	5	7.15	1.27
	5	6	7.47	1.76	6	0.96	0.43	6	6.36	1.94
	30	9	7.21	3.47	9	1.04	0.70	9	6.08	2.92
C	1	6	6.80	1.63	6	0.93	0.46	6	5.74	1.76
	2	4	8.00	2.69	4	1.59	1.35	4	6.28	1.44
	3	6	7.70	1.90	6	1.21	0.40	6	6.44	1.65
	4	6	11.80	4.53	6	2.30	1.93	6	9.32	2.83
	5	6	9.90	3.66	6	1.86	2.06	6	7.86	1.89
	30	8	7.76	2.91	8	1.29	0.93	8	6.39	2.47

Note: See page E-85 for an explanation of the blood parameters and the abbreviations used.

TABLE 3.17
(Continued)

		HD DOSE = LD_{30}					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
B	1	6	1.00	0.00	6	1.00	1.10
	2	6	1.00	0.00	6	0.67	0.82
	3	6	0.83	0.41	6	0.83	0.75
	4	5	1.00	0.00	5	0.20	0.45
	5	6	1.00	0.00	6	0.67	0.82
	30	9	1.00	0.00	9	0.89	0.78
C	1	6	1.17	0.41	6	1.17	0.75
	2	4	1.00	0.00	4	0.75	0.96
	3	6	1.00	0.00	6	0.00	0.00
	4	6	1.00	0.00	6	0.83	0.75
	5	6	1.00	0.00	6	0.50	0.55
	30	9	1.00	0.00	9	0.33	0.71

TABLE 3.17
(Continued)

HD DOSE = LD_{60}

		WBC			ABSSEG			ABSLYMPH		
		N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
GROUP	DAY									
A	1	6	8.22	3.10	6	1.75	1.13	6	6.30	1.92
	2	5	10.44	3.62	5	2.94	2.48	5	7.33	1.13
	3	6	9.37	1.65	6	1.27	0.88	6	7.90	1.51
	4	6	8.20	2.07	6	1.28	1.18	6	6.83	1.93
	5	6	9.83	2.55	6	2.10	1.30	6	7.59	1.74
	30	9	8.80	1.97	9	1.75	1.08	9	6.95	1.62
B	1	6	8.08	2.14	6	1.40	0.99	6	6.49	1.20
	2	6	10.13	3.10	6	1.48	0.84	6	8.52	2.63
	3	6	10.50	3.88	6	2.56	1.90	6	7.71	1.91
	4	6	11.40	3.25	6	2.90	2.03	6	8.42	2.71
	5	6	9.13	3.38	6	1.75	0.92	6	7.22	2.59
	30	9	9.31	2.48	9	2.06	0.98	9	7.16	1.66
C	1	6	8.70	2.49	6	1.46	0.83	6	7.05	2.53
	2	6	10.47	1.98	6	2.00	0.86	6	8.35	1.69
	3	6	8.20	1.62	6	1.45	0.76	6	6.54	1.37
	4	6	9.50	2.89	6	1.33	0.73	6	8.00	2.40
	5	6	9.73	2.03	6	1.99	0.92	6	7.64	1.59
	30	9	9.27	2.24	9	1.58	0.77	9	7.60	2.10

TABLE 3.17
(Continued)

HD DOSE = LD_{60}

GROUP	DAY	MICNORM N	MICNORM MEAN	MICNORM STD	MICPOLY N	MICPOLY MEAN	MICPOLY STD
A	1	6	1.00	0.00	6	0.33	0.52
	2	6	1.00	0.00	6	0.83	0.98
	3	6	1.00	0.00	6	1.00	1.26
	4	6	0.83	0.41	6	0.83	0.75
	5	6	1.00	0.00	6	0.33	0.82
	30	9	1.11	0.33	9	0.44	0.53
B	1	6	1.00	0.00	6	0.33	0.52
	2	6	1.00	0.00	6	0.67	0.82
	3	6	0.83	0.41	6	0.50	0.55
	4	6	1.00	0.00	6	0.33	0.52
	5	6	0.83	0.41	6	0.67	0.82
	30	9	1.00	0.00	9	0.67	0.71
C	1	6	1.00	0.00	6	0.50	0.84
	2	6	1.00	0.00	6	0.17	0.41
	3	6	1.00	0.00	6	0.33	0.52
	4	6	1.00	0.00	6	0.17	0.41
	5	6	1.17	0.41	6	0.67	0.82
	30	9	1.11	0.33	9	0.33	0.50

TABLE 3.17
(Continued)

N = Number of animals
STD = Standard deviation
WBC = White Blood Cells (thousands per $\mu\ell$)
ABSSEG = Absolute Segmented Neutrophils (thousands per $\mu\ell$)
ABSLYMPH = Absolute Lymphocytes (thousands per $\mu\ell$)
MICNORM = Micronucleated Cells/500 Normochromatic Erythrocytes
MICPOLY = Micronucleated Cells/500 Polychromatic Erythrocytes

TABLE 3.18. 12-PARAMETER ANOVA AMONG NO-HD GROUPS TO CHECK FOR TOXICITY OF EACH INHIBITOR ON HEMATOLOGIC VARIABLES

Hematologic Variable:	Inhibitor: 3AB			NIC			NA		
	WBC	ABSLYMPH	ABSSEG	WBC	ABSLYMPH	ABSSEG	WBC	ABSLYMPH	ABSSEG
Parameter									
Intercept	***	***	.	***	***	**	***	***	.
Inhibitor Level	.	.	.	**	*	*	.	.	.
Dosing Day	.	.	.	**	*	.	***	***	***
Level-by-Day	.	.	.	**	*	*	.	.	.
Level^2	.	.	.	.	.	.	.	.	.
Time	.	.	.	.	.	.	.	.	.
Time^2	.	.	.	.	.	.	.	.	.
Time^3	*	*	.	.	.	.	.	.	.
Level-by-Time	.	.	.	.	.	.	.	.	.
Level-by-Time^2	.	.	.	.	.	.	.	.	.
Level^2-by-Time	.	.	.	.	.	.	.	.	.
Level^2-by-Time^2	.	.	.	.	.	.	.	.	.

. $P > 0.05$
* $0.05 > P > 0.01$
** $0.01 > P > 0.001$
*** $0.001 > P > 0.0001$
WBC = White Blood Cells (thousands per $\mu\ell$)
ABSSEG = Absolute Segmented Neutrophils (thousands per $\mu\ell$)
ABSLYMPH = Absolute Lymphocytes (thousands per $\mu\ell$)
3AB = 3-Aminobenzamide
NIC = Nicotinamide
NA = Nicotinic Acid

TABLE 3.19. SUMMARY OF HEMATOLOGIC VARIABLES FOR HD-DOSED GROUPS IN MREF PROTOCOL 19 STUDIES

HD DOSE = LD_{30} INHIBITOR = 3AB

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
D	1	4	2.28	0.63	4	1.36	0.50	4	0.89	0.44
	2	4	2.50	0.35	4	1.46	0.46	4	1.03	0.23
	3	4	0.90	0.35	4	0.16	0.12	4	0.74	0.23
	4	4	1.90	0.74	4	0.09	0.10	4	1.81	0.67
	5	3	2.20	0.87	3	0.11	0.02	3	2.08	0.87
	30	6	8.97	2.05	6	3.71	1.29	6	5.04	1.42
E	1	4	3.10	1.54	4	2.47	1.87	4	0.61	0.37
	2	4	3.10	1.15	4	1.86	0.95	4	1.23	0.29
	3	4	1.00	1.08	4	0.15	0.17	4	0.86	0.92
	4	4	1.00	0.28	4	0.04	0.02	4	0.96	0.27
	5	3	1.27	0.46	3	0.07	0.05	3	1.20	0.41
	30	6	7.90	3.11	6	3.82	2.53	6	3.99	1.03
F	1	4	3.40	0.73	4	2.24	1.14	4	1.08	0.74
	2	4	2.95	0.98	4	2.33	1.04	4	0.61	0.21
	3	4	0.80	0.37	4	0.25	0.19	4	0.55	0.23
	4	4	0.75	0.47	4	0.03	0.01	4	0.72	0.46
	5	4	0.95	0.19	4	0.02	0.01	4	0.93	0.20
	30	6	8.50	2.73	6	3.47	1.73	6	4.80	0.95

Note: See page E-122 for an explanation of the blood parameters and the abbreviations used.

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = 3AB								
			WBC			ABSSEG			ABSLYMPH	
GROUP	DAY	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
G	1	4	3.25	0.75	4	2.02	0.73	4	1.20	0.28
	2	4	4.25	3.44	4	3.48	2.90	4	0.77	0.62
	3	4	0.75	0.57	4	0.22	0.14	4	0.53	0.50
	4	4	1.65	2.38	4	0.14	0.23	4	1.70	2.12
	5	4	0.85	0.38	4	0.02	0.01	4	0.83	0.37
	30	5	8.36	2.41	5	3.84	0.65	5	4.39	1.99
H	1	4	4.30	4.12	4	3.08	3.10	4	1.19	1.17
	2	4	2.65	0.68	4	1.63	0.45	4	1.02	0.31
	3	4	0.95	0.72	4	0.51	0.81	4	0.44	0.23
	4	4	1.15	0.57	4	0.04	0.03	4	1.11	0.55
	5	4	1.45	1.71	4	0.08	0.13	4	1.36	1.55
	30	6	9.07	1.71	6	3.30	0.95	6	5.59	1.12
I	1	4	4.90	2.88	4	3.14	2.44	4	1.74	1.32
	2	4	3.20	0.28	4	1.83	0.60	4	1.37	0.65
	3	4	1.00	0.82	4	0.39	0.24	4	0.61	0.60
	4	4	0.45	0.30	4	0.01	0.01	4	0.44	0.29
	5	3	2.27	2.72	3	0.07	0.04	3	2.17	2.62
	30	6	8.37	3.06	6	3.20	1.54	6	5.04	1.63

TABLE 3.19.
(Continued)

HD DOSE = LD_{30} INHIBITOR = 3AB

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
J	1	4	3.30	0.35	4	2.29	0.75	4	0.97	0.46
	2	4	2.20	0.43	4	1.02	0.29	4	1.18	0.26
	3	4	1.85	1.86	4	0.20	0.18	4	1.65	1.69
	4	4	1.65	0.57	4	0.03	0.02	4	1.62	0.58
	5	3	0.93	0.50	3	0.04	0.03	3	0.89	0.48
	30	6	6.50	1.93	6	2.18	1.23	6	4.17	1.03
K	1	11	3.58	1.26	11	2.09	0.75	11	1.47	0.92
	2	11	3.65	1.67	11	2.10	1.78	11	1.55	1.03
	3	11	1.02	0.56	11	0.32	0.25	11	0.70	0.42
	4	12	1.17	0.68	12	0.03	0.03	12	1.13	0.67
	5	10	1.96	1.20	10	0.05	0.07	10	1.90	1.19
	30	18	9.18	2.70	18	3.87	1.62	18	5.19	1.57

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = 3AB					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
D	1	4	1.00	0.00	4	1.00	0.82
	2	4	1.00	0.00	0	.	.
	3	4	1.50	1.00	0	.	.
	4	4	0.75	0.50	0	.	.
	5	3	1.67	1.15	3	0.33	0.58
	30	6	1.00	0.00	6	0.17	0.41
E	1	4	1.00	0.00	4	2.75	2.87
	2	4	1.25	0.50	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	3	1.00	0.00	1	0.00	.
	30	6	1.00	0.00	6	0.33	0.52
F	1	4	1.00	0.00	4	4.25	2.36
	2	4	1.00	0.00	0	.	.
	3	4	1.50	0.58	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	2	1.50	2.12
	30	6	1.00	0.00	6	0.00	0.00

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = 3AB					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
G	1	4	1.00	0.00	4	3.50	1.00
	2	3	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.25	0.50	2	0.00	0.00
	30	5	1.00	0.71	5	0.00	0.00
H	1	4	1.00	0.00	4	5.25	5.68
	2	4	1.00	0.00	0	.	.
	3	4	1.25	0.50	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.50	1.00	1	1.00	.
	30	6	1.00	0.00	6	0.67	0.52
I	1	4	1.00	0.00	4	1.25	0.50
	2	4	1.00	0.00	2	33.50	3.54
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	1	0.00	.
	30	6	1.00	0.00	6	1.33	0.52

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = 3AB					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
J	1	4	1.00	0.00	4	3.00	2.45
	2	4	0.75	0.50	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.25	0.50	1	0.00	.
	5	3	1.00	0.00	0	.	.
	30	6	1.17	0.41	6	0.50	0.84
K	1	11	1.09	0.30	11	1.36	1.03
	2	11	0.91	0.30	3	21.33	17.62
	3	12	1.00	0.43	0	.	.
	4	12	1.17	0.39	0	.	.
	5	10	1.10	0.32	3	2.00	1.73
	30	18	1.11	0.32	18	0.44	0.62

TABLE 3.19.
(Continued)

HD DOSE = LD_{30} INHIBITOR = NA

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
D	1	2	4.40	1.98	2	2.09	0.41	2	2.31	1.57
	2	2	3.70	0.42	2	2.23	1.37	2	1.47	0.95
	3	2	1.50	0.99	2	0.20	0.08	2	1.30	0.91
	4	2	1.50	1.56	2	0.04	0.02	2	1.46	1.54
	5	4	2.60	1.55	4	0.15	0.14	4	2.45	1.45
	30	4	8.40	3.56	4	4.27	2.99	4	4.05	2.66
E	1	2	2.10	0.99	2	0.96	0.19	2	1.13	0.78
	2	2	2.20	0.85	2	1.33	0.07	2	0.87	0.78
	3	2	1.50	1.27	2	0.12	0.11	2	1.38	1.17
	4	2	1.30	0.99	2	0.02	0.00	2	1.28	0.99
	5	4	1.40	1.08	4	0.02	0.02	4	1.[illegible]	1.08
	30	6	8.07	5.83	6	3.52	3.19	6	4.34	2.64
F	1	2	4.50	0.99	2	1.10	0.01	2	3.33	0.95
	2	2	2.30	0.71	2	1.79	0.67	2	0.51	0.03
	3	2	1.00	0.00	2	0.05	0.00	2	0.95	0.00
	4	2	1.70	0.99	2	0.02	0.01	2	1.68	0.98
	5	4	1.30	0.96	4	0.07	0.09	4	1.23	0.88
	30	5	7.62	1.87	5	3.00	1.65	5	4.54	0.79

TABLE 3.19.
(Continued)

HD DOSE = LD_{30} INHIBITOR = NA

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
G	1	2	2.20	0.00	2	1.21	0.47	2	0.99	0.47
	2	1	3.60	.	1	0.76	.	1	2.84	.
	3	2	2.60	0.28	2	0.51	0.07	2	2.08	0.19
	4	2	1.60	1.13	2	0.04	0.05	2	1.56	1.08
	5	4	1.10	0.62	4	0.03	0.03	4	1.08	0.60
	30	6	9.90	6.99	6	4.23	4.48	6	5.55	3.40
H	1	2	2.60	1.41	2	0.97	0.36	2	1.60	1.04
	2	2	3.10	0.42	2	2.35	0.95	2	0.71	0.47
	3	2	0.60	0.28	2	0.01	0.00	2	0.59	0.28
	4	2	1.30	0.14	2	0.04	0.02	2	1.26	0.12
	5	4	2.05	1.08	4	0.13	0.21	4	1.92	0.90
	30	6	7.82	5.87	6	2.78	1.93	6	4.96	4.06
I	1	2	4.60	2.55	2	1.68	1.07	2	2.89	1.43
	2	2	3.30	0.71	2	1.86	0.22	2	1.44	0.92
	3	2	0.80	0.85	1	0.08	.	1	1.32	.
	4	2	3.00	1.41	2	0.09	0.10	2	2.91	1.32
	5	3	1.73	1.62	3	0.08	0.12	3	1.65	1.50
	30	6	6.47	3.76	6	2.80	2.15	6	3.56	2.10

TABLE 3.19.
(Continued)

HD DOSE = LD_{30} INHIBITOR = NA

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
J	1	2	4.10	3.25	2	1.81	0.88	2	2.25	2.34
	2	2	3.90	0.99	2	2.22	0.38	2	1.68	0.61
	3	2	1.80	1.70	2	0.21	0.22	2	1.58	1.46
	4	2	2.20	1.70	2	0.13	0.15	2	2.07	1.55
	5	4	1.10	0.58	4	0.03	0.03	4	1.07	0.56
	30	4	8.53	3.24	4	3.48	1.69	4	4.86	1.61
K	1	6	3.30	1.70	6	1.32	0.52	6	1.95	1.82
	2	6	2.93	0.35	6	1.70	0.86	6	1.24	0.75
	3	6	1.60	0.81	6	0.36	0.23	6	1.24	0.72
	4	6	1.67	2.05	6	0.05	0.09	6	1.62	1.97
	5	12	1.47	0.88	12	0.03	0.03	12	1.44	0.86
	30	18	5.77	2.90	18	2.43	2.45	18	3.25	1.26

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = NA					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
D	1	4	1.00	0.00	4	4.50	1.73
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	4	0.25	0.50
	30	6	1.17	0.41	6	0.33	0.52
E	1	4	1.00	0.00	4	6.50	3.32
	2	4	1.25	0.50	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	3	0.67	0.58
	30	6	1.00	0.00	6	0.50	0.84
F	1	4	1.00	0.00	4	4.50	3.70
	2	4	1.00	0.00	0	.	.
	3	4	0.75	0.50	0	.	.
	4	4	1.25	0.50	1	2.00	.
	5	4	0.75	0.50	2	0.50	0.71
	30	5	1.60	0.55	5	0.60	0.55

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = NA					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
G	1	4	1.00	0.00	4	4.00	2.16
	2	3	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	1	2.00	.
	5	4	1.00	0.00	1	3.00	.
	30	6	1.00	0.00	6	0.17	0.41
H	1	4	1.00	0.00	4	3.75	2.22
	2	4	1.25	0.50	0	.	.
	3	4	1.25	0.50	0	.	.
	4	4	1.00	0.00	1	1.00	.
	5	4	1.25	0.50	2	1.00	0.00
	30	6	1.00	0.00	6	0.17	0.41
I	1	4	1.25	0.50	4	3.25	1.50
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	3	2.00	1.73	1	2.00	.
	30	6	0.67	0.52	6	0.50	0.55

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = NA					
		MICNORM			MICPOLY		
		N	MEAN	STD	N	MEAN	STD
GROUP	DAY						
J	1	4	1.25	0.50	4	3.00	1.83
	2	4	1.00	0.00	1	9.00	.
	3	4	1.00	0.00	1	2.00	.
	4	4	1.25	0.50	0	.	.
	5	4	1.25	0.50	1	3.00	.
	30	5	1.00	0.00	5	0.60	0.55
K	1	11	1.00	0.00	11	2.18	1.33
	2	12	1.00	0.00	3	29.33	14.57
	3	12	1.17	0.39	0	.	.
	4	12	1.25	0.62	1	3.00	.
	5	12	1.08	0.51	3	0.67	1.15
	30	18	1.00	0.59	18	0.61	0.78

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = NIC								
		WBC			ABSSEG			ABSLYMPH		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
D	1	4	3.55	0.77	4	2.43	0.89	4	1.09	0.38
	2	4	3.50	0.99	4	2.87	1.18	4	0.62	0.54
	3	4	0.85	0.41	4	0.25	0.32	4	0.60	0.19
	4	4	0.60	0.16	4	0.06	0.02	4	0.54	0.17
	5	4	1.25	1.31	4	0.05	0.03	4	1.20	1.30
	30	6	9.67	3.60	6	4.15	1.72	6	5.44	2.99
E	1	4	5.85	1.40	4	3.55	0.94	4	2.26	0.60
	2	4	3.80	1.40	4	2.71	1.53	4	1.09	0.77
	3	4	1.50	1.09	4	0.43	0.40	4	1.08	0.71
	4	4	0.70	0.35	4	0.08	0.07	4	0.62	0.33
	5	4	0.85	0.60	4	0.03	0.02	4	0.82	0.58
	30	6	10.93	6.53	6	3.69	1.64	6	7.14	5.17
F	1	3	3.27	0.46	3	2.51	0.65	3	0.75	0.50
	2	3	3.00	0.72	3	2.36	0.62	3	0.64	0.10
	3	4	1.50	1.99	4	0.81	1.23	4	0.69	0.77
	4	4	1.75	1.18	4	0.21	0.11	4	1.54	1.09
	5	4	2.55	2.29	4	0.34	0.36	4	2.21	1.94
	30	6	8.97	3.41	6	4.35	2.55	6	4.51	1.58

TABLE 3.19.
(Continued)

HD DOSE = LD_{30} INHIBITOR = NIC

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
G	1	4	3.35	1.11	4	2.67	0.52	4	0.63	0.63
	2	4	3.65	1.73	4	2.41	1.53	4	1.24	0.85
	3	4	1.15	0.97	4	0.46	0.68	4	0.69	0.29
	4	4	1.40	1.14	4	0.14	0.19	4	1.26	0.96
	5	4	1.05	0.64	4	0.03	0.02	4	1.02	0.63
	30	6	9.50	4.30	6	3.85	3.19	6	5.47	2.09
H	1	4	4.80	1.78	4	3.50	1.93	4	1.23	1.62
	2	4	4.00	0.71	4	2.40	0.89	4	1.59	1.58
	3	4	1.80	1.78	4	0.68	0.65	4	1.12	1.16
	4	4	1.20	0.99	4	0.11	0.12	4	1.09	0.89
	5	4	0.80	0.57	4	0.04	0.02	4	0.76	0.58
	30	6	12.43	3.66	6	5.64	3.09	6	6.46	2.59
I	1	4	4.45	1.32	4	3.38	1.16	4	1.05	0.76
	2	4	3.60	1.02	4	2.73	1.35	4	0.85	0.47
	3	4	4.55	3.40	4	2.18	1.73	4	2.37	1.68
	4	4	2.80	4.80	4	0.89	1.48	4	1.88	3.28
	5	4	0.85	0.79	4	0.05	0.03	4	0.80	0.76
	30	5	8.76	4.69	5	3.94	2.46	5	4.77	2.29

TABLE 3.19.
(Continued)

HD DOSE = LD_{30} INHIBITOR = NIC

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
J	1	4	5.45	2.32	4	3.88	1.54	4	1.56	1.07
	2	4	3.55	1.33	4	1.61	0.38	4	1.88	1.44
	3	4	2.80	1.57	4	1.25	1.01	4	1.55	0.63
	4	4	1.40	0.75	4	0.18	0.11	4	1.22	0.68
	5	4	1.85	1.51	4	0.17	0.17	4	1.68	1.34
	30	5	7.20	2.60	5	2.68	1.35	5	4.33	1.46
K	1	4	4.00	1.75	4	2.63	1.70	4	1.35	0.86
	2	3	3.33	1.17	3	1.50	0.60	3	1.82	0.62
	3	4	1.55	0.87	4	0.90	0.63	4	0.65	0.67
	4	4	0.55	0.19	4	0.06	0.04	4	0.49	0.21
	5	4	0.50	0.26	4	0.04	0.03	4	0.46	0.24
	30	5	9.12	1.86	5	2.32	0.78	5	6.55	2.56

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = NIC					
		MICNORM			MICPOLY		
		N	MEAN	STD	N	MEAN	STD
GROUP	DAY						
D	1	4	1.25	0.50	4	1.50	1.29
	2	4	1.00	0.00	2	14.00	16.97
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	3	0.00	0.00
	30	6	1.17	0.41	6	0.67	0.52
E	1	4	1.00	0.00	4	2.00	1.63
	2	4	1.00	0.00	0	.	.
	3	4	1.25	0.50	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	3	0.67	1.15
	30	6	1.00	0.00	6	0.17	0.41
F	1	3	1.00	0.00	3	2.67	2.08
	2	3	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.25	0.50	1	2.00	.
	5	4	1.00	0.00	2	1.00	0.00
	30	6	1.00	0.00	6	0.50	0.55

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = NIC					
		MICNORM			MICFOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
G	1	4	1.00	0.00	4	1.00	1.15
	2	4	1.00	0.00	1	0.00	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	2	0.50	0.71
	30	6	1.00	0.00	6	0.50	0.84
H	1	4	1.25	0.50	4	1.75	0.96
	2	4	1.00	0.00	1	44.00	.
	3	4	1.00	0.00	0	.	.
	4	4	0.75	0.50	1	1.00	.
	5	4	1.00	0.00	1	2.00	.
	30	6	1.00	0.00	6	0.17	0.41
I	1	4	1.00	0.00	4	0.75	0.96
	2	4	1.25	0.50	1	54.00	.
	3	4	1.00	0.00	1	1.00	.
	4	4	1.25	0.50	1	1.00	.
	5	4	1.25	0.50	2	0.50	0.71
	30	5	1.00	0.00	5	0.00	0.00

TABLE 3.19.
(Continued)

		HD DOSE = LD_{30} INHIBITOR = NIC					
		MICNORM			MICPOLY		
		N	MEAN	STD	N	MEAN	STD
GROUP	DAY						
J	1	4	1.50	1.00	4	1.50	1.00
	2	4	1.50	1.00	1	29.00	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	3	0.33	0.58
	30	6	1.00	0.00	6	0.17	0.41
K	1	4	1.00	0.00	4	0.75	0.96
	2	3	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	
	5	4	1.00	0.00	0	.	.
	30	6	1.17	0.41	6	0.50	0.55

TABLE 3.19.
(Continued)

HD DOSE = LD_{60} INHIBITOR = 3AB

		WBC			ABSSEG			ABSLYMPH		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
D	1	4	3.65	2.52	4	2.89	2.69	4	0.75	0.67
	2	4	3.85	3.38	4	2.37	1.88	4	1.45	1.55
	3	4	1.15	0.91	4	0.45	0.38	4	0.70	0.54
	4	4	1.00	1.21	3	0.22	0.32	3	1.05	1.01
	5	4	0.80	0.57	4	0.04	0.03	4	0.76	0.54
	30	6	7.57	1.43	6	3.19	1.19	6	4.29	0.96
E	1	4	3.35	0.75	4	2.27	0.74	4	1.05	0.59
	2	4	3.10	0.81	4	1.63	0.42	4	1.46	0.51
	3	4	0.85	0.30	4	0.06	0.04	4	0.79	0.31
	4	4	1.00	0.52	4	0.06	0.04	4	0.94	0.48
	5	4	1.60	1.02	4	0.03	0.02	4	1.57	1.00
	30	6	9.57	1.38	6	4.08	0.76	6	5.37	1.05
F	1	4	2.80	0.67	4	2.05	0.91	4	0.69	0.37
	2	4	1.90	0.60	4	1.40	0.32	4	0.46	0.48
	3	4	0.60	0.33	3	0.16	0.12	3	0.58	0.18
	4	4	0.90	0.48	4	0.03	0.01	4	0.87	0.47
	5	4	1.20	0.75	4	0.07	0.13	4	1.13	0.64
	30	4	10.00	1.23	4	4.34	1.26	4	5.56	1.26

TABLE 3.19.
(Continued)

HD DOSE = LD_{60} INHIBITOR = 3AB

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
G	1	4	4.15	2.02	4	3.72	2.03	4	0.42	0.21
	2	4	2.50	0.96	4	1.71	0.77	4	0.79	0.73
	3	4	0.65	0.30	4	0.10	0.09	4	0.55	0.38
	4	4	0.75	0.47	4	0.02	0.01	4	0.73	0.46
	5	3	1.27	0.12	3	0.02	0.03	3	1.25	0.14
	30	3	7.73	1.51	3	2.55	0.91	3	5.03	0.80
H	1	4	3.60	0.43	4	2.24	0.22	4	1.36	0.58
	2	4	3.50	2.48	4	2.57	2.52	4	0.93	0.43
	3	4	0.70	0.48	4	0.05	0.04	4	0.65	0.48
	4	4	0.50	0.12	4	0.01	0.00	4	0.49	0.11
	5	4	0.65	0.10	4	0.01	0.01	4	0.64	0.11
	30	6	9.13	5.07	6	4.00	3.38	6	5.00	2.00
I	1	4	2.60	0.95	4	1.60	0.80	4	0.38	0.54
	2	4	2.50	0.81	4	1.93	0.83	4	0.57	0.20
	3	4	2.70	2.25	4	1.05	0.70	4	1.59	2.20
	4	4	2.50	0.96	4	0.12	0.10	4	2.38	0.93
	5	4	2.80	3.25	4	0.39	0.71	4	2.39	2.53
	30	6	7.77	1.91	6	2.82	1.97	6	4.84	1.60

TABLE 3.19.
(Continued)

HD DOSE = LD_{60} INHIBITOR = 3AB

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
J	1	4	3.40	0.57	4	2.47	0.48	4	0.86	0.30
	2	4	4.55	1.25	4	2.85	1.66	4	1.70	1.46
	3	4	1.35	1.01	4	0.39	0.23	4	0.96	0.92
	4	4	1.50	1.09	4	0.07	0.04	4	1.43	1.06
	5	4	1.10	0.50	4	0.03	0.02	4	1.07	0.49
	30	5	9.24	3.18	5	4.15	2.42	5	4.94	1.41
K	1	12	4.43	2.40	12	2.69	2.73	12	1.70	1.14
	2	12	2.87	0.87	12	1.80	0.65	12	1.06	0.57
	3	13	1.34	0.84	13	0.31	0.30	13	1.03	0.70
	4	10	1.06	0.93	10	0.05	0.05	10	1.00	0.89
	5	10	0.96	0.67	10	0.02	0.01	10	0.94	0.66
	30	13	7.83	3.06	13	2.74	2.04	13	4.95	1.69

TABLE 3.19.
(Continued)

		HD DOSE = LD_{60} INHIBITOR = 3AB					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
D	1	4	1.00	0.00	4	0.75	0.96
	2	4	1.00	0.00	1	11.00	.
	3	4	0.75	0.50	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	1	2.00	.
	30	6	1.17	0.41	6	0.67	0.52
E	1	4	1.00	0.00	4	1.25	1.26
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	0.75	0.50	0	.	.
	5	4	1.00	0.00	2	0.00	0.00
	30	6	1.17	0.41	6	0.67	0.52
F	1	4	1.00	0.00	4	0.75	1.50
	2	4	1.00	0.00	1	0.00	.
	3	4	0.75	0.50	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	0.75	0.50	1	0.00	.
	30	4	1.00	0.00	4	0.25	0.50

TABLE 3.19.
(Continued)

		HD DOSE = LD_{60} INHIBITOR = 3AB					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
G	1	4	1.25	0.50	4	1.00	0.82
	2	4	1.25	0.50	0	.	.
	3	4	0.50	0.58	0	.	.
	4	4	1.00	0.00	0	.	.
	5	3	0.67	0.58	0	.	.
	30	3	1.00	0.00	3	1.00	0.00
H	1	4	1.00	0.00	4	0.75	0.50
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	0.75	0.50	0	.	.
	5	4	0.75	0.50	1	0.00	.
	30	6	1.00	0.00	6	0.83	0.41
I	1	4	0.75	0.50	4	0.50	0.58
	2	4	1.00	0.00	2	11.00	5.66
	3	4	1.00	0.00	1	0.00	.
	4	4	1.00	0.00	1	0.00	.
	5	4	1.00	0.00	3	0.67	0.58
	30	6	1.00	0.00	6	0.50	0.84

TABLE 3.19.
(Continued)

		HD DOSE = LD_{60} INHIBITOR = 3AB					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
J	1	4	1.00	0.00	4	0.25	0.50
	2	4	1.00	0.00	0	.	.
	3	4	0.75	0.50	0	.	.
	4	4	1.00	0.82	0	.	.
	5	4	1.00	0.00	0	.	.
	30	5	1.00	0.00	5	0.60	0.55
K	1	12	1.00	0.00	12	0.42	0.67
	2	12	1.08	0.29	1	0.00	.
	3	13	0.92	0.28	0	.	.
	4	12	0.83	0.39	0	.	.
	5	11	1.00	0.00	3	1.00	0.00
	30	13	1.00	0.00	13	0.31	0.48

TABLE 3.19.
(Continued)

HD DOSE = LD_{60} INHIBITOR = NA

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
D	1	4	5.85	1.12	4	4.17	1.09	4	1.56	0.49
	2	4	5.30	1.87	4	2.93	2.37	4	2.37	2.52
	3	4	0.95	0.75	4	0.23	0.25	4	0.72	0.53
	4	4	0.60	0.37	4	0.03	0.02	4	0.57	0.35
	5	4	0.75	0.60	3	0.02	0.03	3	0.91	0.58
	30	6	11.13	1.74	6	5.22	2.55	6	5.77	1.80
E	1	4	3.40	2.07	4	1.73	0.77	4	1.62	1.94
	2	4	3.05	0.57	4	1.59	0.80	4	1.46	0.87
	3	4	1.10	0.81	4	0.27	0.38	4	0.83	0.48
	4	4	0.63	0.67	4	0.06	0.03	4	0.56	0.64
	5	4	1.05	0.98	4	0.03	0.03	4	1.02	0.96
	30	6	7.80	2.47	6	3.04	1.89	6	4.66	1.28
F	1	4	3.70	1.01	4	1.80	0.82	4	1.88	0.27
	2	4	3.20	1.19	4	2.02	1.23	4	1.18	0.46
	3	4	1.30	1.04	4	0.16	0.15	4	1.14	0.91
	4	4	0.45	0.38	3	0.02	0.01	3	0.51	0.41
	5	4	0.95	0.41	4	0.05	0.05	4	0.90	0.39
	30	6	11.03	4.99	6	5.54	3.63	6	5.28	1.87

TABLE 3.19.
(Continued)

HD DOSE = LD_{60} INHIBITOR = NA

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
G	1	4	5.45	2.87	4	3.63	3.72	4	1.80	1.91
	2	4	2.45	1.54	4	1.69	1.26	4	0.76	0.35
	3	4	0.80	0.95	4	0.14	0.22	4	0.66	0.75
	4	4	0.70	0.60	4	0.04	0.06	4	0.65	0.54
	5	4	2.65	2.74	4	0.20	0.35	4	2.45	2.42
	30	6	10.00	2.61	6	3.90	1.17	6	5.97	2.15
H	1	4	3.70	1.55	4	1.78	0.40	4	1.92	1.54
	2	4	3.15	0.53	4	2.39	0.35	4	0.76	0.48
	3	4	1.05	0.44	4	0.26	0.28	4	0.79	0.41
	4	4	0.35	0.19	4	0.01	0.01	4	0.34	0.18
	5	4	0.75	0.47	4	0.03	0.03	4	0.72	0.48
	30	6	8.20	2.30	6	3.55	1.38	6	4.56	1.14
I	1	4	3.90	1.88	4	2.78	1.88	4	1.11	1.56
	2	4	2.80	1.21	4	1.28	0.21	4	1.50	1.04
	3	4	1.00	0.49	4	0.22	0.12	4	0.78	0.41
	4	4	0.60	0.37	4	0.02	0.01	4	0.58	0.36
	5	4	0.80	0.57	4	0.05	0.05	4	0.75	0.52
	30	6	7.93	3.46	6	3.74	2.47	6	4.08	2.23

TABLE 3.19.
(Continued)

HD DOSE = LD_{60} INHIBITOR = NA

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
J	1	4	3.80	0.82	4	2.66	0.88	4	1.14	0.06
	2	4	3.15	0.84	4	2.28	1.07	4	0.87	0.24
	3	4	1.20	1.23	4	0.25	0.30	4	0.95	0.96
	4	4	0.50	0.35	4	0.03	0.02	4	0.47	0.33
	5	4	0.80	0.63	4	0.06	0.06	4	0.74	0.57
	30	6	9.70	1.92	6	5.44	1.87	6	4.17	1.61
K	1	12	3.78	1.34	12	2.63	1.38	12	1.14	0.71
	2	10	3.70	1.16	10	2.53	1.06	10	1.16	1.01
	3	12	0.87	0.95	12	0.17	0.18	12	0.70	0.77
	4	12	0.70	0.52	11	0.01	0.01	11	0.73	0.51
	5	10	1.04	0.95	9	0.04	0.03	9	1.09	0.92
	30	14	11.27	2.24	14	5.22	2.12	14	5.90	1.74

TABLE 3.19.
(Continued)

		HD DOSE = LD_{60} INHIBITOR = NA					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
D	1	4	0.75	0.50	4	0.75	0.96
	2	4	1.00	0.00	0	.	.
	3	4	1.25	0.96	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	1	0.00	.
	30	6	1.00	0.00	6	0.17	0.41
E	1	4	1.00	0.00	4	2.75	1.50
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	2	0.00	0.00
	30	6	1.00	0.00	6	0.83	0.98
F	1	4	1.00	0.00	4	3.75	3.59
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.82	1	2.00	.
	5	4	1.00	0.00	3	0.33	0.58
	30	6	1.00	0.00	6	0.83	0.75

TABLE 3.19.
(Continued)

HD DOSE = LD_{60} INHIBITOR = NA

GROUP	DAY	MICNORM N	MICNORM MEAN	MICNORM STD	MICPOLY N	MICPOLY MEAN	MICPOLY STD
G	1	4	1.25	0.50	4	2.75	2.22
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	2	0.50	0.71
	30	6	1.00	0.00	6	0.33	0.52
H	1	4	1.25	0.50	4	1.25	1.26
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.25	0.50	0	.	.
	5	4	1.00	0.00	1	0.00	.
	30	6	1.00	0.00	6	0.00	0.00
I	1	4	1.00	0.00	4	0.75	0.96
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	2	0.50	0.71
	30	6	1.00	0.00	6	0.83	0.75

TABLE 3.19.
(Continued)

		HD DOSE = LD_{60} INHIBITOR = NA					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
J	1	4	1.00	0.00	4	1.25	0.96
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.00	0.00	1	0.00	.
	30	6	1.00	0.00	6	0.33	0.52
K	1	12	1.08	0.29	12	1.17	1.19
	2	10	1.20	0.42	0	.	.
	3	12	1.08	0.29	0	.	.
	4	12	1.08	0.29	0	.	.
	5	11	1.09	0.30	2	0.50	0.71
	30	14	1.07	0.27	14	0.50	0.65

TABLE 3.19.
(Continued)

HD DOSE = LD_{60} INHIBITOR = NIC

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
D	1	4	4.15	2.66	4	1.84	1.31	4	2.27	2.75
	2	4	3.50	0.90	4	2.08	0.86	4	1.42	0.98
	3	4	0.95	0.19	4	0.40	0.12	4	0.55	0.15
	4	4	2.80	4.40	4	0.55	1.01	4	2.25	3.39
	5	3	0.93	0.76	3	0.03	0.01	3	0.91	0.76
	30	6	10.17	3.19	6	4.61	2.42	6	5.42	2.17
E	1	4	3.10	1.42	4	2.00	1.32	4	1.05	0.48
	2	3	3.07	0.76	3	2.48	0.53	3	0.57	0.30
	3	4	0.60	0.28	4	0.18	0.18	4	0.42	0.30
	4	3	1.20	1.25	3	0.15	0.16	3	1.05	1.09
	5	4	1.20	0.82	4	0.07	0.05	4	1.13	0.76
	30	5	8.92	2.15	5	3.86	2.04	5	4.95	1.92
F	1	3	4.67	2.50	3	3.95	2.65	3	0.71	0.57
	2	4	2.40	1.40	4	1.92	1.05	4	0.48	0.37
	3	3	0.53	0.31	3	0.10	0.01	3	0.44	0.31
	4	4	0.45	0.50	4	0.06	0.05	4	0.39	0.45
	5	1	0.40	.	1	0.03	.	1	0.37	.
	30	3	11.60	2.95	3	6.64	2.22	3	4.72	1.08

TABLE 3.19.
(Continued)

HD DOSE = LD_{60} INHIBITOR = NIC

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
G	1	4	3.25	1.43	4	2.57	1.24	4	0.66	0.44
	2	3	2.47	0.81	3	1.73	0.94	3	0.73	0.52
	3	4	0.95	0.87	4	0.46	0.85	4	0.49	0.24
	4	4	0.70	0.66	4	0.04	0.03	4	0.66	0.64
	5	3	0.53	0.23	3	0.02	0.01	3	0.51	0.22
	30	2	9.80	2.26	2	5.84	1.42	2	3.90	0.77
H	1	3	4.33	2.42	3	3.25	2.78	3	1.07	0.46
	2	3	2.67	0.42	3	1.89	0.50	3	0.78	0.22
	3	4	0.75	0.34	4	0.20	0.10	4	0.54	0.35
	4	4	0.65	0.38	4	0.05	0.01	4	0.60	0.39
	5	3	1.00	1.04	3	0.19	0.28	3	0.81	0.76
	30	6	8.90	2.28	6	3.89	1.91	6	4.77	1.81
I	1	4	4.45	1.61	4	3.01	1.48	4	1.40	0.94
	2	1	2.60	.	1	1.43	.	1	1.17	.
	3	4	2.45	3.57	4	0.72	1.24	4	1.73	2.33
	4	4	0.35	0.19	4	0.05	0.03	4	0.30	0.17
	5	3	1.73	2.32	3	0.35	0.57	3	1.33	1.68
	30	6	9.13	2.27	6	4.43	0.84	6	4.57	2.72

TABLE 3.19.
(Continued)

HD DOSE = LD_{60} INHIBITOR = NIC

GROUP	DAY	WBC N	WBC MEAN	WBC STD	ABSSEG N	ABSSEG MEAN	ABSSEG STD	ABSLYMPH N	ABSLYMPH MEAN	ABSLYMPH STD
J	1	4	4.48	1.16	4	3.39	1.36	4	1.05	0.50
	2	3	3.27	1.03	3	2.79	0.84	3	0.47	0.26
	3	4	0.90	0.48	4	0.32	0.32	4	0.58	0.43
	4	4	0.85	0.64	4	0.11	0.11	4	0.74	0.53
	5	4	0.75	0.19	4	0.03	0.03	4	0.72	0.19
	30	6	7.60	1.33	6	3.07	0.35	6	4.46	1.25
K	1	3	4.87	2.21	3	3.82	2.03	3	1.04	0.33
	2	4	2.35	1.08	4	1.70	0.76	4	0.65	0.46
	3	4	0.75	0.34	4	0.15	0.13	4	0.60	0.22
	4	4	0.80	0.54	4	0.07	0.05	4	0.73	0.54
	5	2	0.70	0.14	2	0.02	0.01	2	0.68	0.13
	30	4	8.00	2.83	4	3.03	1.90	4	4.80	1.03

TABLE 3.19.
(Continued)

		HD DOSE = LD_{60} INHIBITOR = NIC					
		MICNORM			MICPOLY		
		N	MEAN	STD	N	MEAN	STD
GROUP	DAY						
D	1	4	1.00	0.00	3	1.00	1.00
	2	4	1.00	0.00	1	84.00	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	1	2.00	.
	5	3	1.00	0.00	3	0.00	0.00
	30	6	1.17	0.41	6	0.33	0.52
E	1	4	1.00	0.00	4	4.50	2.65
	2	3	1.00	0.00	1	70.00	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	4	1.25	0.50	3	1.00	0.00
	30	5	1.00	0.00	5	0.60	0.55
F	1	3	1.00	0.00	3	1.67	1.15
	2	4	1.75	0.96	1	16.00	.
	3	4	1.00	0.00	0	.	.
	4	4	1.50	0.58	0	.	.
	5	1	1.00	.	0	.	.
	30	3	1.00	0.00	3	1.00	1.00

TABLE 3.19.
(Continued)

		HD DOSE = LD_{60} INHIBITOR = NIC					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
G	1	4	1.00	0.00	4	2.50	1.29
	2	4	1.00	0.00	0	.	.
	3	4	1.25	0.50	0	.	.
	4	4	1.50	0.58	0	.	.
	5	3	1.33	0.58	1	1.00	.
	30	2	1.00	0.00	2	0.50	0.71
H	1	3	1.00	0.00	3	2.00	2.00
	2	4	1.00	0.00	0	.	.
	3	4	1.25	0.50	0	.	.
	4	4	1.50	1.00	0	.	.
	5	4	1.00	0.00	2	2.00	0.00
	30	6	1.00	0.00	6	1.17	0.75
I	1	4	1.00	0.00	4	2.00	1.15
	2	2	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.25	0.50	0	.	.
	5	3	1.33	0.58	1	2.00	.
	30	6	1.17	0.41	6	0.33	0.52

TABLE 3.19.
(Continued)

		HD DOSE = LD_{60} INHIBITOR = NIC					
		MICNORM			MICPOLY		
GROUP	DAY	N	MEAN	STD	N	MEAN	STD
J	1	4	1.00	0.00	4	3.25	2.06
	2	4	1.00	0.00	1	5.00	.
	3	4	1.00	0.00	0	.	.
	4	4	1.25	0.50	0	.	.
	5	4	2.50	3.00	2	1.00	1.41
	30	6	1.00	0.00	6	0.67	0.52
K	1	3	1.00	0.00	3	1.00	0.00
	2	4	1.00	0.00	0	.	.
	3	4	1.00	0.00	0	.	.
	4	4	1.00	0.00	0	.	.
	5	2	2.00	1.41	0	.	.
	30	4	1.00	0.00	4	0.75	0.96

N = number of animals
STD = standard deviation
WBC = White Blood Cells (thousands per $\mu\ell$)
ABSSEG = Absolute Segmented Neutrophils (thousands per $\mu\ell$)
ABSLYMPH = Absolute Lymphocytes (thousands per $\mu\ell$)
MICNORM = Micronucleated Cells/500 Normochromatic Erythrocytes
MICPOLY = Micronucleated Cells/500 Polychromatic Erythrocytes
. = could not be calculated either because all data were missing or (in cases of standard deviations)
because the sample size was 1
3AB = 3-Aminobenzamide
NIC = Nicotinamide
NA = Nicotinic Acid

TABLE 3.20. RESULTS OF ANOVA MODEL FOR THE EFFECTS OF TOTAL AMOUNT OF INHIBITOR ADMINISTERED AMONG THE HD-DOSED GROUPS BY EXPERIMENT

		Target HD Dose					
		LD_{30}			LD_{60}		
	Inhibitor:	3AB	NIC	NA	3AB	NIC	NA
Effect	Variable						
Inhibitor	WBC	.	.	.	.	.	*
	ABSLYMPH	.	.	.	.	.	.
	ABSSEG	.	.	.	.	.	.
Inhibitor^2	WBC	.	.	.	.	.	*
	ABSLYMPH	.	.	.	.	.	.
	ABSSEG	.	.	.	.	.	*
Inhibitor^3	WBC	.	.	.	.	.	.
	ABSLYMPH	.	.	.	.	.	.
	ABSSEG	.	.	.	.	.	.
Inhibitor-by-Time	WBC	.	.	.	.	.	.
	ABSLYMPH	.	.	.	**	.	.
	ABSSEG	.	.	.	.	.	.
Inhibitor-by-Time^2	WBC	.	.	.	.	.	.
	ABSLYMPH	.	*	.	*	.	.
	ABSSEG	.	.	.	.	.	.
Inhibitor^2-by-Time	WBC	.	.	.	.	.	.
	ABSLYMPH	.	.	.	*	.	.
	ABSSEG	.	.	.	.	.	.
Inhibitor^2-by-Time^2	WBC	.	.	.	.	.	.
	ABSLYMPH	.	.	.	.	.	.
	ABSSEG	.	.	.	.	.	.

TABLE 3.20.
(Continued)

.	= P > 0.05
*	= 0.05 > P > 0.01
**	= 0.01 > P > 0.001
WBC	= White Blood Cells (thousands per $\mu\ell$)
ABSSEG	= Absolute Segmented Neutrophils (thousands per $\mu\ell$)
ABSLYMPH	= Absolute Lymphocytes (thousands per $\mu\ell$)
3AB	= 3-Aminobenzamide
NIC	= Nicotinamide
NA	= Nicotinic Acid

Note: Significant squared effects imply a quadratic relationship of the blood variable with the effect; cubed effects, although not significant, were included to check for cubic relationships between the variable and the effect.

TABLE 3.21. RESULTS OF ANOVA MODEL FOR THE EFFECTS OF INHIBITOR LEVEL AND REGIMEN ADMINISTERED AMONG THE HD-DOSED GROUPS BY EXPERIMENT

		Target HD Dose					
		LD_{30}			LD_{60}		
	Inhibitor:	3AB	NIC	NA	3AB	NIC	NA
Effect	**Variable**						
Level	WBC	.	.	.	.	.	*
	ABSLYMPH	.	.	.	.	*	.
	ABSSEG	.	.	.	.	.	.
Regimen	WBC	.	.	.	.	.	.
	ABSLYMPH	.	.	.	.	.	.
	ABSSEG	.	.	.	.	.	.
Level-by-Regimen	WBC	.	.	.	.	.	**
	ABSLYMPH	.	.	.	.	*	.
	ABSSEG	.	.	.	.	.	**

. $P > 0.05$
* $0.05 > P > 0.01$
** $0.01 > P > 0.001$
WBC = White Blood Cells (thousands per $\mu\ell$)
ABSSEG = Absolute Segmented Neutrophils (thousands per $\mu\ell$)
ABSLYMPH = Absolute Lymphocytes (thousands per $\mu\ell$)
3AB = 3-Aminobenzamide
NIC = Nicotinamide
NA = Nicotinic Acid